DO POST-SURGICAL UNILATERAL CLEFT LIP AND PALATE PATIENTS HAVE A COMPARABLE DYNAMIC FACIAL EXPRESSION TO A NON-CLEFT POPULATION?

by

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Abstract

Aim: The aim of this study was to determine if the dynamic movement of the naso-labial region was similar between cleft adult patients, at the end of their treatment journey, and an age and gender matched control group.

Design: Single centre, case-controlled study

Materials and methods: Thirteen participants, who met the specific inclusion criteria, were invited voluntarily to be imaged performing a maximum smile using a 3D facial motion capture system. The control group was selected consisting from a larger pool of 54 male and 54 female non-cleft volunteers, previously imaged using the same system. Images were re-orientated according to the principle planes, and 17 landmarks were digitally placed and automatically tracked, 4 were used for stabilisation and the remainder for analysis. The x, y and z co-ordinates of the tracked landmarks were used to analyse the magnitude of displacement of bilateral structures either side of the midline and to calculate the path of motion of the bilateral structures. Mesh tracking was used to produce an asymmetry score to assess the shape of the mouth and / nose when mirrored onto itself around the clinical midline, and when trying to achieve the best fit using Procrustes analysis at rest, mid-smile and a maximum smile.

Results: Maximum displacement of right and left corners of the mouth, in the x, y, z direction and Euclidian distance were statistically significantly ($p<0.05$) less in the cleft group (20-40% less) compared to the control group during maximum smile. This was greater than 3mm, therefore clinically significant. There was a baseline level of asymmetry in the control group (range 0.7-0.9mm), as right and left corners of the

mouth did not follow the same path of motion. This difference was larger in the cleft group (range 1.0-2.0mm). At each time point, the asymmetry score of the lips when smiling and reflecting around the clinical midline was statistically significantly more ($p<0.05$) in the cleft group compared to the control group. When assessing the symmetry of the lips using Procrustes superimposition, the difference between the two groups was statistically significant ($p<0.05$) at rest and median smile, however not statistically significant at maximum smile.

The alar bases were displaced statistically significantly less ($p<0.05$) in the z direction in the cleft group (1.2mm) compared to the control group (2.1mm), and was clinically significant when assessing the alar base of the affected cleft side. The path of motion of the alar bases was similar in both groups. During smiling, the asymmetry score of the alar base, was statistically significantly higher when reflected around the clinical midline then when using Procrustes superimposition for cleft patients ($p<0.001$) at each time point, compared to the control group. At maximum smile, there was less displacement of right and left cristae philtre, in the x, y, z direction and Euclidian distance, for the cleft group compared to the control group. The affected cleft side moved statistically significantly less ($p<0.05$) in the x and z-direction. There was a baseline level of asymmetry of path of motion of the right and left crista philtre demonstrated in the control group, with a greater degree of difference present in the cleft group.

Conclusions: There was statistically ($p<0.05$) and clinically significantly (>3mm) less displacement (Euclidian distance) of the corners of the mouth in cleft patients compared to the control group. The corners of the mouth did not follow the same path of displacement. There was an increase in asymmetry score of the corners of the

mouth and alar bases from rest to maximum smile. As the asymmetry scores were larger using the clinical midline rather than the Procrustes method, this would suggest that the lips were similar in shape but orientated differently in the face of cleft patients compared to non-cleft individuals.

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CHAPTER 1

LITERATURE REVIEW

1.1 The human face

The human face has always been a significant focus of scientists, medical professionals and artists. It allows an individual to interact with another person and their environment, can give information about the health status of an individual and is used for identification. Genetic and environmental factors are combined to form the unique composition of a human face; it is made up of osseous, cartilaginous, soft tissue and dental elements (Sforza *et al*., 2013). The face is traditionally divided into three parts; the upper, mid and lower face. The anatomical features are precisely functionally and structurally organised so that the face plays its role in identity, aesthetic and expressive functions (Marur, 2014).

1.1.1 Facial beauty and balance

It was thought that the beauty of facial appearance is determined by symmetry and harmony of proportions. The ideal proportions are based on the “divine proportion”, which was initially described by mathematician Fra Luca Pacioli (cited by Baker and Woods, 2001). This is the division of a line so that the smaller line to the larger line is the same ratio as the larger line to the whole line. This ratio can be expressed mathematically as 1:1.618. There have been suggestions that the proportions were already used by the Greeks in architecture, particularly by the sculptor Phidas (Cook, 1914). The divine proportion has also previously been named as the “Phi” ratio. A method of facial analysis was performed by Ghyka (1946), in which numerous measurements agreed with the concept of the divine proportion (Ghyka, 1946). Ricketts (1982) described links between the divine proportion and the biological significance, specifically relating these theories to beauty and facial aesthetics. He discovered that divine ratios existed when reviewing numerous facial landmarks using

ten photographs of models from magazines, at random. Radiographically, he analysed 30 lateral cephalograms described to have an “ideal occlusion”, revealing at least eight divine proportions linked to the cranial base and facial skeleton. (Ricketts, 1982). After this, the use of the divine proportions was suggested as a guide for planning for orthognathic surgery. Baker *et al*. (2001) investigated this by testing the hypothesis that aesthetic improvement after orthodontic and orthognathic surgical treatment could be related to the divine ratio proportions (Baker and Woods, 2001). However, based on pre and post treatment lateral cephalometric images and clinical photographs, no correlation was found between the aesthetic rating and divine proportion. The study did however highlight the fact that the treatment may not have actually been planned to achieve these divine proportions, and should therefore be viewed with caution. The study concluded that the concept of divine proportions should be only used as a guide, alongside conventional established treatment planning methods. It is possible for beautiful faces not to demonstrate ratios in the divine proportion and vice versa. In general, faces which are considered to be attractive have a general harmony amongst numerous measurements, with their ratios approaching the divine proportions. Langlois and Roggman (1990) explored what constitutes beauty, by digitising male and female faces, averaging them mathematically, and had them judged by three hundred raters to identify the attractiveness of the computer-generated images as well as the individual faces. Their findings suggested that attractive faces were those that represented the characteristics close to the mean of the population (Langlois and Roggman, 1990). Many cultures have defined aesthetic criteria to fulfil, but the actual existence of defined facial ratios in “attractive” subjects is still regularly debated. Studies therefore still progress to define, on a quantitative basis, facial attractiveness (Rossetti *et al*., 2013).

1.1.2 Facial attractiveness

There is no identified gold standard for facial beauty. Similarly, attractiveness may include a combination of characteristics, including symmetry, averageness, youthfulness, sexual dimorphism, good grooming and pleasant expressions (Rhodes, 2006). Generally, most studies tend to rate "attractiveness", assuming that there are common aesthetic characteristics for both sexes with responses correlating directly to desirability to date or finding a partner (Cunningham *et al*., 1990).

The basis of physical attractiveness is commonly linked to a persons' preference on choosing a potential partner. Though documented centuries ago by philosophers and writers, it was a concept explored in more detail in a controlled study (Walster *et al*., 1966). Four individuals rated 752 university students in terms of physical attractiveness, and links were made with attractiveness and social desirability. Authors of the study did however highlight that a major limitation was that the students were only permitted a few seconds for raters to assess the subjects, with minimal interaction. When considering biologically based preferences, alongside averageness of faces and sexual dimorphism, facial symmetry has been highlighted as a trait associated with facial attractiveness (Rhodes, 2006).

1.1.3 Facial symmetry

Previous studies have previously demonstrated that facial symmetry is a determinant for identifying a suitable partner (Watson and Thornhill, 1994; Thornhill and Gangestad, 1996). It has been proposed by evolutionary biologists that a preference for symmetry should also be adaptive, as it is an indicator of genetic and health quality (Thornhill and Møller, 1997). Symmetry has therefore been regarded as one of the

primary factors of facial attractiveness (Rhodes, 2006). Attractiveness is said to be reduced if the level of asymmetry is greater, and also if the asymmetry is closer to the midline (Springer *et al*., 2007). There is however lack of scientific evidence for the range or value at which facial asymmetry becomes aesthetically unacceptable (Meyer-Marcotty *et al*., 2011). There have been studies confirming that faces do not exhibit bilateral symmetry (Mulick, 1965; Burke, 1971; Gilbert and Bakan, 1973). In 1981, Farkas and Cheung took clinically landmarked facial measurements using callipers on a group of 6-18-year olds to investigate asymmetries. There were three defined age groups: 6, 12 and 18-year-olds. Measurements were taken from six paired projective points and was defined as asymmetric if there was a 2mm or greater difference between the two sides. They concluded that although not as obvious, asymmetries were common (Farkas and Cheung, 1981).

1.1.4 Fluctuating asymmetry

Fluctuating asymmetries are small non-directional (random) deviations from perfect symmetry, in paired bilateral traits (Rhodes, 2006). It is commonly used as an index of development stability, as it is seen as the organism's ability to resist developmental disturbances and stressors. Origins of developmental disturbance maybe genetic e.g. mutations, or environmental e.g. toxins, pathogens, nutritional (Parsons, 1990; Møller and Swaddle, 1997). In humans, body fluctuating asymmetry can be related to premature birth, inbreeding, mental retardation and psychosis (Livshits and Kobyliansky, 1991). The accumulation of the asymmetries across the lifetime of the organism is thought to depend not only on the extent to which an organism has been exposed to perturbations, but its own ability to withstand them, i.e. developmental stability. In a study by Grammer and Thornhill, fluctuating asymmetry has been used

as an index of developmental stability, including being used in evolutionary psychological studies for sexual preference (Grammer and Thornhill, 1994). The study was the first to demonstrate that facial symmetry has an effect on positive judgements linked to facial attractiveness, however their statistically significant findings were based on a small sample size of only 16 participants. From this, there have been functional explanations to state that facial symmetry is a predictor of attractiveness in males and females (Perrett *et al*., 1999; Pound *et al*., 2014). More recent research by Khambay *et al*., (2019) has quantified fluctuating asymmetry of dynamic smiles in a group of normal individuals using 3D motion capture technology, enabling calculation of a facial asymmetry score to be produced as a baseline measure. This study was successful in detecting that a smile becomes more asymmetric over the duration of the smile in a group of normal individuals (Khambay *et al*., 2019).

1.2 Cleft lip and palate

The most common craniofacial deformity is an oral cleft, accounting for 15% of all congenital abnormalities (Shapira *et al*., 1999). Cleft lip and/or palate (CLP) is often an immediately recognisable disruption of normal facial structure. A cleft lip is a separation in the upper lip and can also involve the gingivae. It can affect one side of the lip (unilateral) or both sides (bilateral). Depending on the extent, it can present as a small separation in the lip (incomplete cleft) or can continue on into the base of the nose (complete cleft). If the palate is involved, it can include some or all of the hard palate, and the soft palate. Clefts of the lip and palate can occur as a joint or separate entity.

CLP can cause significant morbidity to affected children, and can pose a significant financial burden for families, as well as a societal burden, though it is not a major cause of mortality in developed countries (Wehby *et al*., 2006; Wehby and Cassell, 2010). Individuals affected by CLP can experience difficulties with feeding, hearing, speaking and social integration (Dixon *et al*., 2011a).

1.2.1 Embryological development of the lip and palate

Intricate co-ordination of programmes for cell migration, growth, differentiation and apoptosis all contribute to the development of the lip and palate. Neural folds give rise to neural crest cells, which migrate through mesenchymal tissue and contribute to the developing craniofacial region. In the 4th week of embryonic development, the neural crest cells help to form the paired maxillary and mandibular prominences, and the frontonasal prominence, which surround the primitive oral cavity. By the end of the 4th week, ectodermal thickenings form the nasal placodes dividing the lower part of the frontonasal prominence into the medial and lateral processes. The medial nasal processes merge with one another alongside the maxillary processes on each side in the 6th week of development, leading to the formation of the upper lip and primary palate. Just before this is completed, there is peaking of cell division of the lateral nasal process which makes it vulnerable to teratogenic insult. Failure of the closure mechanism can occur if there is any disturbance at this critical time point.

During the 6th week of development, the secondary palate develops when paired palatal shelves form from an outgrowth of the maxillary process. Initially, they grow in a vertical direction, alongside the developing tongue. It is in the 7th week that the palatal shelves assemble horizontally above the tongue, and fuse when they come

into contact. This forms a midline epithelial seam that eventually disintegrates to allow continuity of mesenchymal tissue along the palate. Bony and muscular elements are then formed from the palatal mesenchyme, which correspond to the position of the hard and soft palate. By the 10th week of development, the secondary palate fuses in the midline, as well as with the primary palate and nasal septum. This therefore results in the division of the oral and nasal cavity into separate spaces, which allows respiration and mastication to take place simultaneously (Mossey *et al*., 2009; Sperber, 2002).

1.2.2 Epidemiology

The average occurrence of CLP is said to be 1 in 700 live births, and considered to be higher in Asia (1 in 500) and lowest in Africa (1 in 2500). Cleft palate (CP) has an incidence of 1 in 1500 new-born babies and does not have a large variation with geographical location. Cleft lip (CL) tends to be unilateral 80-85%, with the majority being right sided clefts 67%. There is a 2:1 male to female ratio for cleft lip, and 1:2 male to female ratio for cleft palate (Dixon *et al*., 2011a). 70% of all CLP cases are considered to be non-syndromic, and the remainder of the cases form part of a range of 500 syndromes.

1.2.3 Aetiology

Genetics and environmental predisposing factors contribute to the aetiology of oral clefts (World Health Organization, 2002). Due to the complex developmental mechanism involved in CLP, a broad base of research has been reviewed to understand the causative factors.

1.2.3.1 Environmental factors

Research involving identification of environmental factors as a contributor to the aetiology of oral clefts has been challenging, as cleft studies ideally require prospective cohort data with the additional access to genetic data to be conclusive (Dixon *et al*., 2011b). Habits such as maternal smoking has been linked with a higher risk of both cleft lip ± palate, as well as isolated cleft palate, to a high population-attributable risk of 20% (Little *et al*., 2004; Honein *et al*., 2007). Passive exposure to smoking however has not been included in research in most studies, therefore this figure may be underestimated (Mossey *et al*., 2009). Consumption of alcohol has been linked to a positive association in orofacial clefts in some studies (Romitti *et al*., 1999; Bille *et al*., 2007) but not all (Romitti *et al*., 2007; Meyer *et al*., 2003). As consumption of alcohol has the potential to be associated with other confounding factors (e.g. stress, drugs, smoking) due to its use in varying social contexts, results of studies have been found to be variable (Mossey *et al*., 2009).

Multivitamin supplements such as folic acid have been linked to a reduction in prevalence of orofacial clefts, however a 2008 meta-analysis discussed that the possible correlation may be confounded by other positive lifestyle factors linked to multivitamin use (Johnson and Little, 2008). The importance of zinc is recognised in

foetal development and links with zinc deficiencies and orofacial clefts have been noted in studies in the Philippines and the Netherlands (Krapels *et al*., 2004; Tamura *et al*., 2005). Anti-epileptic agents, such as phenobarbital, diazepam, and phenytoin have been associated with increased risk of craniofacial anomalies (Dravet *et al*., 1992; Abrishamchian *et al*., 1994), as well as maternal corticosteroid use (Park-Wyllie *et al*., 2000). Nutritional and metabolic deficiencies have also been suggested as being causative, such as low folic acid, obesity and diabetes (Setó-Salvia and Stanier, 2014).

1.2.3.2 Genetic factors

The different inheritance patterns in CLP and CP can be due to either genetic heterogeneity (mutations in different genes), or allelic heterogeneity (different mutations in the same gene). Some genes may play a part in both types of clefting, this is because similar developmental processes occur during primary and secondary palatal development. Some mutations in the same gene result in a mixture of CP or CLP including IRF6 (Van der Woude syndrome), FGFR1 (Kallman syndrome), and MSX1 (orofacial clefts and hereditary tooth agenesis) (Lidral and Murray, 2004).

Familial clustering studies and twin studies have provided strong evidence to suggest that there is a genetic component to non-syndromic CLP; however most appear sporadic and few studies show well defined Mendelian inheritance (Jugessur *et al*., 2009). It has been suggested that genetic risk factors have minimal individual impact, but they may interact with environmental risk factors, forming a multifactorial model of inheritance (Dixon, *et al*., 2011). Genome-wide linkage and association studies have been successful in identifying specific gene loci that are associated with CLP. Due to

advances in genomics, there have been significant advances in identifying the causative gene mutations in syndromic CLP (Stanier and Moore, 2004). However, due to the genetic heterogeneity, moving away from the Mendelian inheritance pattern, and the need for large data sets and expensive genomics tools, it has been more difficult to understand non-syndromic CLP (Dixon *et al*., 2011a). Gene loci including regions on chromosomes 1, 2, 4, 6, 14, 17 and 19 (MTHFR, TGFA, D4S175, F13A1, TGFB3, D17S250, and APOC2) have been suggested to have a causal role in cleft lip and palate (Mossey *et al*., 2009).

1.2.4 Surgical correction of CLP

The surgical repair of a cleft lip and palate is normally carried out in the early months and years of life, in order to improve facial function and aesthetics (Madahar *et al*., 2013). As CLP patients can have either or both functional and aesthetic concerns, they may require input from numerous specialities for correction; this can include surgery, speech and language therapy, dental treatment and psychosocial interventions. In the early few months of life, highly specialised operations are required to improve the function of the oropharynx and the aesthetics of the face and continues from birth to adulthood. Considering the affected oral structures, it is vital that patients are also committed to a lifetime of maintenance of good oral health. Intervention begins in the first few months of life with perinatal nursing care soon followed by a surgical procedure, with operations continuing on throughout the younger years until adulthood (Colbert *et al*., 2015). Due to the nature of the deformity, involving either or both the lip and palate, there has previously been debate over timing of surgical procedures due to facial growth of this cohort of patients (Normando *et al*., 1992).

A French dentist, Le Monnier, reportedly completed the first cleft palate closure in 1766 (cited by James *et al*., 2014). Subsequently, additional surgeons were said to have advanced on treatment of the oral deformities such as work from Von Langenbeck (1861), Von Graefe (1820), Dieffenbach (1826), and Veau (Veau and Borel, 1931). Despite early successful post-operative results with modern procedures and new incision techniques, patients still developed facial asymmetries, requiring secondary alveolar bone grafting and orthognathic surgery. Patients who had been treated with early palatoplasties, in their first year of life, commonly resulted in restricted maxillary growth, severe scarring and velopharyngeal insufficiency (James *et al*., 2014). However, the justification for early surgical intervention was to assist in normal speech development (Anastassov and Joos, 2001). Surgical procedures were normally carried out between 10-20 months of age with either one or two-stage procedures (Von Langenbeck, 1861; Veau and Borel, 1931; Furlow, 1986; Kriens, 1970). Stage one, often referred to as a lip adhesion, is usually performed around the age of 10 weeks, followed by stage two, six weeks later (James *et al*., 2014). Previously, research has tended to focus on the technique or timing of palatoplasty, and how speech compares after using various surgical procedures. However, there are a lack of studies that report on speech outcomes for CLP patients (Peterson-Falzone, 1996). Comparisons between studies is difficult as many investigations do not use a standardised outcome measure (Sell *et al*., 2001).

1.2.5 Diversity of clinical management

Within the UK, differences were found in the timing of surgical intervention and in which sequences the lip and palate were operated on. More commonly, the lip and anterior palate were repaired at the age of 2-3 months, as the primary procedure,

followed by closure of the soft palate at 4-12 months of age, once the airway was more secure (Goodacre and Swan, 2012). One of the most difficult aspects of cleft management, is deciding between early or later repair of the hard palate and the effect on palatal growth versus speech development (Colbert *et al*., 2015). The most popular method of closure of the palate was reported to be the method described by von Langenbeck (Von Langenbeck, 1861) advocating simple closure of the palate, other less popular methods involved raising a palatal flap Veau (Veau and Borel, 1931) and Wardill (Wardill, 1937) (Asher-McDade and Shaw, 1990). These methods however can result in more disturbance to the soft tissue of the hard palate, causing potential bony defects and subsequent scar tissue, all of which can have negative effects on facial growth (Markus *et al*., 1993).

Repair of the lip requires lengthening of the greater segment margin, with a rotation advancement being the most popular (Sitzman *et al*., 2008). A primary nasal tip correction is often advocated at the stage of primary lip repair. Surgeons now advocate subperiosteal dissection of muscle away from the maxilla, as this is believed to generate more bone and minimise deep seated scar tissue (Anastassov and Joos, 2001). Surgical advances that are thought to improve long-term outcome include avoiding incisions around the base of the lateral nostril margin, minor corrections of the lip scar with interposition of small flaps above the white roll, and should be within the vermillion mucosa (Goodacre and Swan, 2012).

Following lip repair, current practice suggests that repair of the palate is performed around the time that the child begins to phonate. The risks of an insufficient repair should always be balanced with the benefits. Due to the inability to close off the

oropharynx from the nasopharynx, a patient with cleft palate is often unable to produce phonemes. During child development, children tend to learn sounds and mimic what they hear around them from their parents or siblings, so if incorrect articulation habits are acquired, they are often difficult to correct after this point. Due to this, it is often preferred to perform the earliest feasible repair. One of the major drawbacks however is palatal scarring. This can cause restriction of growth of the maxilla in all three directions, subsequently resulting in iatrogenic maxillary deficiency (Hopper *et al*., 2014; Shi and Losee, 2015). In order to achieve a balance between the two outcomes, the palatoplasty is often carried out at 1 year of age (James *et al*., 2014).

In a number of centres, alveolar bone grafting of cancellous bone is also carried out before the eruption of the permanent canines (Asher-McDade and Shaw, 1990). This is because the bony deformity in the alveolar ridge is not corrected by the primary cleft repair. The timing of the procedure is usually determined by the orthodontist, and is closely related to dental maturity. It offers the best opportunity to close any remaining oronasal fistulas in the anterior palate, and is commonly carried out between the ages of 7 to 11 years. Bone is normally grafted from the iliac crest or tibial plateau, and the cleft bony line is reopened and the mucosal-lined cavity is packed with chips of grafted bone. The procedure is normally effective, and often allows good progression of arch correction by the treating orthodontist (Goodacre and Swan, 2012). The study by Åbyholm *et al*., reviewed the clinical and radiographical advantages gained from 80 patients with clefts repaired using cancellous bone grafts, with an observation time of 17 - 44 months. Advantages to this treatment included stabilisation of the maxillary segments, better bone support for teeth adjacent to the cleft and residual gaps in the dental arch were able to be closed orthodontically in 80% of the clefts. Best results

were achieved when the permanent canine erupts through the grafted site, in close proximity to the incisor, and was shown to induce alveolar bone generation. Other benefits included improvement in nasal asymmetry, better support for the depressed alar base, effective closure of oronasal fistulae, and conclusion of orthodontic treatment at a similar time to non-cleft patients. Serious complications have included infection within the grafted sites, causing loss of grafts and subsequent failure of the graft (Åbyholm *et al*., 1981).

Despite the benefits of early treatment, a certain proportion of children with CLP will develop secondary maxillary hypoplasia following primary surgical repair. Often these patients require surgical maxillary advancement procedures alongside orthodontic alignment (Asher-McDade and Shaw, 1990). Mobilising the maxilla as a procedure originates back to more than 150 years ago. In 1859, Von Langenbeck proposed the use of a maxillary osteotomy to assist in removal of a nasal polyp (Von Langenbeck, 1859). Following this and Cheever's work in 1870 to down fracture the hemi maxilla in order to remove a nasal obstruction; both had the same idea to relieve the maxilla from its fixed position (Cheever, 1870). Orthognathic surgery uses controlled bone cuts, "osteotomies", in patterns described by Le Fort (Le Fort, 1901). Continuing surgical advancements have shown the versatility of a Le Fort I osteotomy to correct maxillary deformities (Sullivan, 2016). Fixed appliances are usually advocated to level and co-ordinate the arches prior to orthognathic surgery. Due to the effects of growth, any orthognathic procedures are usually deferred until late teenage years once growth has ceased (Asher-McDade and Shaw, 1990).

1.2.6 Cleft care in the UK

In the late 90's, cleft care in the United Kingdom was relatively dispersed and had multiple local services providing cleft care. Compared to the best Scandinavian centres, growth outcomes in the UK were found to be poor. Following a review by the Craniofacial Society of Great Britain and Ireland, it was agreed that an urgent review of the structure and organisation of the cleft service was required (Shaw *et al*., 2001; Shaw *et al*., 2005). In addition to this, suggestions were made to improve surgical training of treatment of cleft patients; a large number of cleft teams existed, but were poorly organised (Colbert *et al*., 2015). Despite recommendations of the centralisation of cleft care, there was a professional divide between maxillofacial and plastic surgeons (Sandy *et al*., 2001). As a result of this, a national review was instigated by the government, Clinical Standards Advisory Group (CSAG), under Professor John Murray (Shaw *et al*., 2001).

1.2.7 Clinical Standards Advisory Group (CSAG)

The CSAG study was carried out with an aim of establishing and standardising the levels of specialist care in order to provide a protocol for the minimum level of care. In specific, the study looked to assess the quality of care of children in the UK, born with complete UCLP, and the quality of the training of the healthcare professionals providing the care (Williams *et al*., 2001). 5-year olds and 12-year olds with complete unilateral cleft lip and palate were sampled, in order to demonstrate a range of outcomes indicative of the cleft care they had received. Five-year olds were chosen for the study to review the outcome of primary surgery; at this stage they would have had no exposure to orthodontics or bone grafting therapies. The "Five-Year Old Index" was used to specifically determine the outcomes of dental arch relationships at the

age of five years, at which point it was early enough to look at what different outcomes were present as a result of variations in clinical practice (Atack *et al*., 1997). The 12-year old group was chosen for the study so that facial growth and the success of secondary alveolar bone grafting could be assessed, in addition to the records taken at 5 years old.

Data for 457 patients was collected in the form of dental study models, lateral cephalometric and anterior occlusal radiographs, photographs, an oral health assessment, patient satisfaction questionnaire and audio-visual speech recording (Sandy *et al*., 2001). It was reported that dental occlusion and facial growth was deemed to be poor for 40% of the sample, and that a large proportion of these would require orthognathic surgery in their later years. Less than 60% of the secondary alveolar bone grafts undertaken were successful; demonstrating a low success rate of alveolar bone grafting in the UK (Williams *et al*., 2001). Clinically, this meant that children were more likely to require a repeat operation to correct the deficiency, or risk having a compromised dentition. A significant factor was that bone grafting was not being carried out at the ideal time (aged 9-11 years, when the root of the contra-lateral canine is two-thirds formed); 15% of children in the sample had not received a graft by the age of 12-14 years, condemning them to a worse prognosis. There was no suitable objective outcome measure to effectively assess nasolabial appearance; but there was good interrater reliability when subjectively assessing facial attractiveness. Dental health of cleft patients was also seen to be very similar to that of the general population, suggesting that cleft teams need to further improve the dental health of cleft patients, especially as excellent oral hygiene is usually required for patients in the complex cleft care pathway (Williams *et al*., 2001).

The CSAG study accepted that the use of static photographs to assess the nasolabial complex was not ideal (Williams *et al*., 2001), even though the nasolabial complex is highly involved in a range of dynamic facial expressions, including smiling. The appearance of the lip, nose and profile were judged based on the Asher-McDade system due to the good interexaminer agreement previously reported (Asher-McDade *et al*., 1991). Primary surgery for the lip, close after birth is usually based for both functional and aesthetic reasons for CLP patients. However, the objective dynamic functional capacity of the nasiolabial region is not often an outcome measure and the criteria for a satisfactory repair is primarily based on subjective assessment of movement of the nasolabial complex (Trotman, 2011), which has been shown to be unreliable in some studies (Ritter *et al*., 2002; Trotman *et al*., 2007). Facial movement and smile dynamics is vital when assessing the aesthetics of a smile as described by Rubenstein, who discussed the importance of dynamic facial expressions having an impact on social interaction and attractiveness (Rubenstein, 2005). The dynamic nature of facial expression is important in non-verbal communication, such as emotions and observations. This emphasises the importance of identifying standardised and objective methods to assess the dynamics of the nasiolabial complex (Lin *et al*., 2013).

The CSAG report also presented speech outcomes in UCLP patients using a modified version of the Cleft Audit Protocol for Speech (CAPS). Three specific outcomes were assessed: consonant errors, nasality and intelligibility. The study found that over half of 5-year olds and nearly 20% of 12-year olds had speech that had low intelligibility, despite the majority of them having speech therapy. A large proportion of them had a

history of velo-pharyngeal incompetence (VPI), with many of patients not undergoing secondary corrective surgery. The study concluded that despite children having primary surgery, poor speech outcomes were being achieved and the provision of speech therapy being provided was not meeting the needs of the children (Sell *et al*., 2001).

1.2.8 Outcome measures

As the cleft pathway in the United Kingdom has seen a number of changes within the last 15 years, it has been increasingly important to use outcome measures which are valid and reliable. In order to be useful, outcome measures should be easy to carry out, quick, and require minimal training (Jones *et al*., 2014). As various specialties are involved in the cleft care pathway, they each have their own method of recording outcome measures. When evaluating aesthetic outcome measures, there is no universally accepted method or agreed standard (Sharma *et al*., 2012). To record or demonstrate success of a particular intervention, new outcome measures are constantly being developed. Unfortunately, due to the complexity of different types of cleft, the same outcome measures are not universally applicable, as the care pathway includes different interventions or treatments. Current literature generally reports on UCLP patient outcome measures, as they include both palate and lip defects, and can therefore account for outcomes across all of cleft care (Jones *et al*., 2014).

1.2.8.1 Dento-alveolar assessment

To assess primary surgery and facial growth, the Great Ormond Street London and Oslo Norway Yardstick (GOSLON Yardstick) outcome measure was developed (Mars *et al*., 1987). The index uses study models of patients around the age of 12 years old

in their early permanent dentition, and assesses the anteroposterior arch relationships, vertical labial segment relationships, and transverse relationships (Mars *et al*., 1987). Outcomes are categorised into five groups; Excellent (with little or no treatment required), Good, Fair, Poor and Very Poor (orthognathic surgery required if satisfactory occlusal relationships are to be achieved). An advantage of the index is that study models are scored in the early permanent dentition and if there are any occlusal and skeletal problems they will already be evident. In addition, the index aims to score the severity of the malocclusion based on the ease or difficulty of the correction required. Disadvantages of the index are that clinicians must be trained and calibrated to use this outcome measure and it is only applicable to UCLP patients.

If a patient, in the early permanent dentition, has already had a course of orthodontic treatment or a secondary bone grafting procedure, an incorrect GOSLON score may be recorded as secondary interventions have already been carried out in addition to the primary surgery. Therefore, to provide an earlier outcome measure of primary surgery, the 5 Year Olds Index was developed (Atack *et al*., 1997). Similar to the GOSLON Yardstick, study models are used for the assessment, but at aged 5 years. In addition, the 5 Year Olds Index retained the format of the five categories to grade the severity of the malocclusion. It has been successful as an outcome audit tool, however, as with the GOSLON yardstick, clinicians require training and calibration before it can be used and is restricted for use for UCLP patients. Other indices have been developed, such as the Modified Huddart/Bodenham scoring system (Huddart and Bodenham, 1972) and the EURCRAN index (Fudalej *et al*., 2011). However, the GOSLON Yardstick index is the most popular and the 5 Year olds Index is commonly used with the younger cohort of patients (Jones *et al*., 2014).

1.2.8.2 Dental

Occlusal outcome measures are scored using the Peer Assessment Rating (PAR) (Richmond *et al*., 1992b), which uses percentage of improvement of the occlusion from pre to post treatment in the permanent dentition. PAR uses the concept of assigning a score to various occlusal traits (Richmond *et al*., 1992a), then uses two methods of assessment of improvement: 1) a reduction in the weighted PAR score and 2) assessing the percentage reduction in the weighted PAR score. This was designed to demonstrate the improvement relative to the pre-treatment score. Using PAR, despite some deficiencies, it remains the most reliable and valid (Richmond *et al*., 1992a; Buchanan *et al*., 1993), and is still used for cleft patients treated in the UK (Deacon *et al*., 2007).

1.2.8.3 Alveolar bone grafting

Currently, outcomes for alveolar bone grafting are predominantly assessed using plane radiographs. Based on these radiographs three outcome measures have been shown to demonstrate similar reproducibility (Nightingale *et al*., 2003). These are post-operative interdental bone height (Bergland *et al*., 1986), amount / percentage of bony infill at the cleft site pre and post bone graft (Kindelan *et al*., 1997) and the position of the bone within the cleft in relation to the full length of the root surfaces adjacent to the cleft and cleft midline (Chelsea Scale and Grade) (Witherow *et al*., 2002). Outcome scoring based on 2D images will be affected by image reliability and quality, magnification and distortion, superimposition of structures, and difficulties in identifying clear landmarks (Posnick *et al*., 1993). Given the lack of volumetric data, more recent studies are assessing the outcomes of alveolar bone grafting using three-dimensional volumetric analyses, i.e. CBCT (Oberoi *et al*., 2009).

1.2.8.4 Speech

Speech function is assessed by indices such as the Great Ormond Street Speech Assessment (GOS, SP, ASS), which aims to provide extensive information on speech defects (Sell *et al*., 1994; Grunwell, 1999). However, the index has proven to be very detailed and time-consuming for auditing purposes (John *et al*., 2006). Although speech is assessed from the age of 18 to 24 months, formal outcome measures for speech are not obtained until the age of 5. The cleft audit protocol for speech assessment (CAPS-A) has been devised for auditing purposes, and consisted of recorded patient audio and video clips, which were then rated on pre-determined scales by specialist Speech and Language therapists (John *et al*., 2006). Speech deficiencies were rated on nasality, intelligibility, and consonant production. Results were then presented as a traffic light system, with red indicative of a poor result. Multiple trained examiners are required to ensure reproducibility and reliability; as it is a process that requires consensus listening, which can be a costly and time-consuming process. Further research is required to determine the cost-effectiveness of consensus listening (Jones *et al*., 2014).

1.2.8.5 Nasolabial region appearance

Appearance of the nasolabial region is of great interest, as it is suggested to be one of the most important outcome measures determining the success of CLP treatment (Roberts *et al*., 1991) and can be assessed either directly or indirectly (Sharma *et al*., 2012). Direct assessment is carried out in the clinic, however there are many more options if assessment is performed indirectly. Indirect methods include clinical photographs (Asher-McDade *et al*., 1991), black and white drawings, videotapes, projected cinefilms and computer-generated images (Howells and Shaw, 1985; Pigott

and Pigott, 2010). Once appropriate images have been obtained, they are either analysed quantitively or qualitatively. Scales, index, ranking or scoring systems can be used to subjectively evaluate facial appearance based on the assessment of various facial features. Whereas quantitative assessment uses linear or angular measurements to provide an objective evaluation of facial appearance when reviewing different surgical techniques. Five main scoring systems have been used: Asher-McDade system (Asher-McDade *et al*., 1991), VLS classification (Assuncao, 1992), cranio-facial proportion indices (Edler *et al*., 2010), the aesthetic index (Johnson and Sandy, 2003) and the cleft lip evaluation profile (CLEP) index (Ohannessian *et al*., 2011). The Asher-McDade system uses cropped clinical photographs of the nasolabial region, and utilises a five-point scale, ranging from excellent to very poor appearance. Four features are assessed and include frontal nasal appearance, nasal symmetry, nasal profile and shape of the vermillion border including the upper lip. As there are only 5 points on the rating scale, there is generally a higher level of inter-rater agreement (Jones *et al*., 2014). The scale is relatively fast and easy to use as it assesses the outline of the lip and nose (with exception of nasal symmetry). The system can evaluate individual components or collectively provide a total assessment of the repaired cleft. It has successfully been validated in assessing outcomes of surgical CLP treatment (Jones *et al*., 2014). The VLS (vermillion, lip, scar) classification is derived from three scores, where each component (vermillion, lip, scar) is assessed, making the classification quick and easy to use (Assuncao, 1992). Its use has been reported widely, however it has not been validated. The other three scoring systems, cranio-facial proportion index, the aesthetic index and the cleft lip evaluation profile (CLEP) index are all relatively simple to use, however are less commonly used and lack validity.

After a review by Darzi (Department of Health, 2008), the importance of patient satisfaction was highlighted- however there is currently a lack of outcome measures to support satisfaction and quality of life for cleft patients (Jones *et al*., 2014).

1.3 Aesthetic outcomes and imaging techniques

Previously, facial form has been investigated using two-dimensional (2D) imaging such as plane radiographs and photographs, however these methods fail to record information in the third dimension. In addition, 2D images are associated with greater errors magnification and positioning errors (Posnick *et al*., 1993). There are several static facial cleft lip and palate aesthetic outcome measure rating systems, which have been broadly divided into four categories by Sharma *et al*., (2012) in their systematic review; direct clinical assessment (Assuncao, 1992) clinical photographic evaluation (Asher-McDade *et al*., 1991), clinical videographic assessment (Morrant and Shaw, 1996) and three-dimensional evaluation (Meyer-Marcotty *et al*., 2010). Despite having internationally validated outcome measures for facial growth and speech in cleft lip and palate patients, there is no accepted system to assess the outcome of dynamic facial aesthetics.

1.3.1 Direct clinical assessment

Direct clinical assessment allows subjective real-time assessment of patients in four dimensions, however logistically, inter-rater reliability is not possible (Sharma *et al*., 2012). Indices like the VLS classification do not consider the facial profile or the nose. Plaster casts of the mid-face have been used to record angular and linear facial measurements (Friede *et al*., 1980). However it was not deemed to be practical for routine clinical use due to patient compliance and the methodology of obtaining these

facial casts (Friede *et al*., 1980; Sharma *et al*., 2012). In addition, the measurements taken are Euclidean distances and as such do not quantify 3D changes in a landmark position. However despite these short comings, comparative studies have been published using direct clinical measurements on cleft patients (Farkas *et al*., 1993).

1.3.2 Clinical photography

The benefits of using conventional photographs for evaluation of cleft repairs are that numerous validated scoring systems have been developed, such as the Asher-McDade system (Asher-McDade *et al*., 1991), the Craniofacial Index (Edler *et al*., 2010) and the Facial Impairment Scale (Tobiasen and Hiebert, 1994). However, all of these indices are limited to static observations. Evaluation based on clinical photographs offers quick and cheap methods of assessment, however they can be affected by poor quality photos, lack of standardisation, and irregular positioning or cropping of photos. They are also unable to detect dynamic discrepancies that would otherwise be identified on direct clinical observation or by video capture. It is also worth noting that 2D measurements have been shown to underestimate the true 3D measurements by as much as 43% (Gross *et al*., 1996).

1.3.3 Static three-dimensional (3D) imaging

Following technological advances numerous studies have reported on the use of 3D surface imaging to assess the outcomes of cleft repair (Wong *et al*., 2008; Meyer-Marcotty *et al*., 2010; Al-Omari *et al*., 2003). Three-dimensional evaluation appeared to show promise with increased accuracy, validity and reproducibility but was not without its problems (Meyer-Marcotty *et al*., 2010). It was shown that some scanning system, for example FaceScan, was less accurate when capturing areas around the

nasal cavities, columella and upper lip due to camera positioning and shadowing. Despite the precision and objective measurements obtainable, this technology has not been routinely clinically accepted as an outcome assessment tool, most likely due to equipment cost and complex statistical methods of analysis. There is lack of consensus on which system to use due to variation in cost, ease of use, validation and reproducibility between the different imaging systems. The non-ionising nature of the imaging however makes this technique an attractive option to quantify facial morphology and symmetry. A recent systematic review based on 33 papers investigated the modalities of assessment of non-ionising 3D images in quantifying facial morphology, symmetry and appearance in cleft lip and palate patients, found that the large volume of data gathered can be susceptible to operator bias when analysing the findings. They recommended that there was potential to use an automated mapping strategy to minimise operator bias and analysis, and increase reliability (Thierens *et al*., 2018).

1.3.4 Dynamic imaging

1.3.4.1 Video capture

Clinical videographic assessment, based on conventional video recordings, has been used to appreciate any deficiencies in function and movement, in addition to aesthetics. However, scoring systems and technical variations meant this method did not provide an adequate level of reproducibility (Sharma *et al*., 2012). A previous study based on a sample of 30 children with CLP has assessed video recordings in relation to aesthetics; the study concluded that changes in lip symmetry were significantly different between rest and speaking; the videos were scored using a modified Asher-McDade system (Morrant and Shaw, 1996). The study lacked reliability, was more

time consuming compared to assessing clinical photographs, as well as losing clarity of clinical features due to poor technical quality (Sharma *et al*., 2012).

1.3.4.2 Three-dimensional motion (4D) imaging

Further advances were identified in the study by Trotman (2000) where dynamic facial recordings of three seconds, with markings on patient's faces, were superimposed onto pre-selected craniofacial landmarks. A modified Procrustes approach was used to statistically analyse shapes by scaling, rotating or moving them on top of each other to minimise the differences. Calculations were made to create global asymmetry scores, based on the difference of displacement of the pre-determined landmarks. The study concluded that CLP patients scored higher when assessing facial asymmetry; it also highlighted the importance of assessing dynamic motion using the Procrustes analysis (Trotman *et al*., 2000).

1.3.4.2.1 Marker-based tracking systems

Marker-based tracking systems use pre-placed retro-reflective markers and video recordings to track facial motion. Gross *et al*. (1996) used ExpertVision Flextrak software (Motion Analysis Corporation, Santa Rosa, California) to compare the amplitude of facial motion obtained using three-dimensional and two-dimensional images (Gross *et al*., 1996). The motion capture system used small reflective markers (2 or 5mm in diameter) with a centred hole for accuracy of placement, on 15 anatomical facial landmarks. Although the authors described the use of facial motion they only used the rest and maximum expression frames, this could have been achieved using a static 3D imaging system. The issue with using a marker based system is that the markers may interfere with the facial expression as they are foreign

items placed on facial landmarks, potentially obscuring the true landmark point (Popat *et al*., 2010; Ju *et al*., 2016). In an attempt to overcome this different sized markers have been used, 3mm (Trotman, 2011), 4mm (Weeden *et al*., 2001; Trotman and Faraway, 1998) and different adhesives including original rubber-based (Trotman *et al*., 1998) or eyelash adhesives (Trotman *et al*., 2005).

Green and Wilson (2006) used a video-based movement tracking system (Vicon 250, Vicon Motion Systems, 2000), which also uses reflective markers positioned on the face, capturing at 60 frames per second, and five infrared video cameras (Green and Wilson, 2006). This study was successful in capturing 3D movement, movement speed, and movement duration of the markers in a cross section of infants. Another system used by Hontanilla and Auba (2008) consisted of three infrared cameras with facial markers (FACIAL CLIMA). This system was able to measure angles, points, vectors and velocities between facial landmarks. The system was also stated to be accurate to 0.41º and 0.13mm, with 0.94 - 0.95 intra-reliability and 0.9 inter-reliability (Hontanilla and Aubá, 2008). A recent study reported on the use of an optoelectronic 3D motion analyser, and eight round 2mm reflective markers (SMART-E system, BTS S.p.a, Garbagnate Milanese, Italy) to record verbal and non-verbal facial expressions of 20 adults deemed to have “clinically normal facial function” (Sidequersky *et al*., 2016).

1.3.4.2.2 Marker-free systems

Marker-free systems obviously do not use retro-reflective markers to track facial landmarks, but instead use alternative methods. Mishima *et al*., published a series of studies which used an “active stereophotogrammetry” system (Mishima *et al*., 2004,

2006, 2014). The system projections an infra-red structured pattern onto the target subjects face, and uses three infra-red video cameras to capture face movement and a colour video camera to record the facial texture. Prior to capture the three digital video cameras were calibrated with a checkerboard cube and controlled by a synchronising signal generator (Imagenics SG-701, Tokyo, Japan). The system captured 30 frames per second and was used to capture facial movements of three patients with bilateral cleft lip and palate (Mishima *et al*., 2004). Points were tracked automatically using an optical flow and template matching technique (Jo and Tsuji, 1998). This system was technologically advanced and required several complex pieces of hardware. Even though the whole face was captured during the video sequence, only the information related to the markers could be extracted and analysed.

A more recent example of active stereophotogrammetry is the 3dMDfaceTM Dynamic System (3Q Technologies, Atlanta, GA, USA). It has been widely used in studies to capture static / dynamic facial expressions of healthy individuals and orthognathic surgery patients (Popat *et al*., 2008a, 2011, 2010, 2008b, 2012). A white light is projected onto the face, as well as a random infra-red speckle projection, and both are captured simultaneously, at 48 frames per second. Ten, high volume image files (three-dimensional geometry definition files) are produced per static image, which accompanying software helps to generate thousands of three-dimensional points of the face using complex algorithms (Popat *et al*., 2008a). This time the whole face is captured as a “wire-frame” but up for vertices and corresponding facial texture.

More recently 3D motion capture (4D imaging) techniques have been developed to evaluate dynamic facial movement based on “passive stereophotogrammetry”. This is a non-invasive, reliable and fast method of objectively evaluating the dynamics of facial movements (Shujaat *et al*., 2014; Trotman, 2011; Trotman *et al*., 2013; Lowney *et al*., 2018; Al-Rudainy *et al*., 2018). This system does not require any infra-red cameras or infra-red projections but instead uses the skin features i.e. pores and texture to triangulate the image and recover depth. The Di4D system (Dimensional Imaging Ltd., Glasgow) captures images from two pods consisting of three video cameras (one colour and two monochrome video cameras) producing high resolution images, at 60 frames per second, as a passive 3D motion capture system. A lighting system is used to highlight the face, and the 4D capture is processed on a PC (Al-Anezi *et al*., 2013; Ju *et al*., 2016). Di4D software then analyses the video sequence data, and accurately pinpoints each pixel through each frame using optical flow. This automatic tracking method ensures that identified surface points were corresponding to the same surface point in previous and subsequent frames, and demonstrated that automatic tracking of facial landmarks during facial animation is accurate to 0.55mm (Al-Anezi *et al*., 2013). Subsequent studies have followed on to analyse facial expression using Di4D due to its high level of clinical accuracy; in normal control groups (Ju *et al*., 2016; Lowney *et al*., 2018a; Khambay *et al*., 2019), oncology patients (Shujaat *et al*., 2014) and in children with clefts and patients with facial palsy (Alagha *et al*., 2018; Hallac *et al*., 2017; Gattani *et al*., 2020).

1.4 Reproducibility of facial expressions

During normal daily routine, the lip and nasal areas are rarely static when in function i.e. during speech, mastication and non-verbal communication or facial expression. Although static asymmetry in UCLP patients has been documented (Bell *et al*., 2014), expression asymmetry of the orofacial morphology during social interactions is likely to be more relevant. Social interaction involves verbal and non-verbal expression; Popat *et al*. (2010) concluded that words such as “puppy” produced a higher level of reproducibility than non-verbal expression such as a lip purse or a maximum smile (Popat *et al*., 2010). The study reported the outcomes using principle components analysis (PCA), which is statistically meaningful but does not translate well into a clinical outcome. Using the word “puppy” produced and allowed analysis of the labial region only and did not allow pan-facial assessment. In order to assess if an intervention has had a clinically significant effect, the facial animation must be reproducible (Lowney *et al*., 2018). Johnston *et al*. (2003) studied the reproducibility of five facial expressions amongst thirty subjects, and assessed the intra and inter-session reproducibility using static 3D images (Johnston, 2003). The study concluded that rest position was most reproducible. Using individual landmarks, advances by Ju *et al*. (2016) demonstrated that the maximum smile expression had the highest reproducibility, having the least difference in magnitude, speed and similarity at different time intervals, but also demonstrated a good range of displacement of facial landmarks. Grimacing was found to be the least reproducible facial expression, possibly due to patients finding it difficult to perform this expression (Ju, 2016).

1.5 Cleft lip and palate and facial asymmetry

Surgical correction of the CLP however does not always result in restoration of satisfactory facial aesthetics and these patients are often left with a residual facial asymmetry. A study by Bugaighis *et al*. (2010) investigated the facial morphological variation of children with unilateral/bilateral cleft lip and/or palate using the 3dMD system, and found that compared to a matched control group, there was a significant difference in symmetry. The study also demonstrated that there is a level of asymmetry in aesthetically pleasing faces. A power calculation was carried out to determine the sample size, however the study collected data on all types of cleft and compared them to the control group. Despite demonstrating residual asymmetry in a large number of cleft patients, it did not encompass the dynamic nature of facial expression, and only included paediatric patients between 8-12 years old. Many three-dimensional motion (4D) studies have investigated the surgical facial aesthetic outcomes of children with cleft lip and palate pre-and post-surgery (Al-Rudainy *et al*., 2017; Hallac *et al*., 2017; Gattani *et al*., 2020), however there is limited literature involving 4D imaging based on adults with CLP. Under the current cleft care pathway, many patients still continue to require surgery once facial growth is complete, to address residual hard tissue/soft tissue defects (Madahar *et al*., 2013; Taib *et al*., 2015; Colbert *et al*., 2015). Wong *et al*. (2018) compared 3D stereophotogrammetric images of 16 adult UCLP patients with non-cleft patients, and found that many nasolabial characteristics which were present after a primary UCLP repair continue on into adulthood. This study did not however investigate any dynamic facial movements. Few studies have investigated the outcome of adult patients at the end of their treatment journey, including following orthognathic surgery. It is only truly after this point that a patient's facial profile and function are corrected at a hard tissue level, which therefore affects the resulting soft

tissue morphology. Despite having outcome measures for specific elements of facial aesthetics for CLP patients, e.g. nasolabial appearance, there are currently no validated, objective outcome measures reviewing the overall dynamic facial expression for CLP patients.

1.6 Summary of literature review

The appearance of the human face allows individuals to interact with others and their environment and can also provide an insight into an individual's health status. Facial attractiveness may include a number of characteristics including symmetry, youthfulness, averageness and sexual dimorphism (Rhodes, 2006). Symmetry is regarded as a key factor of facial attractiveness; asymmetry however is common amongst the general population, and becomes more apparent during the course of smile (Khambay *et al*., 2019). Individuals with a known facial asymmetry, such as cleft, facial deformity or facial paralysis patients, are known to have various treatments and surgical procedures throughout their lives in order to minimise any underlying facial asymmetry, and aim to correct any clinically significant differences. Cleft patients have been shown to have completed their cleft treatment journey with residual facial asymmetry (Wong *et al*., 2018). Despite being a widely researched topic with numerous outcome measures reported, there has been no internationally agreed aesthetic objective outcome measure to quantify facial asymmetry (Sharma *et al*., 2012). Early 3D imaging techniques had still been prone to information loss (Gross *et al*., 1996), particularly in areas prone to shadowing e.g. around the nasiolabial complex (Meyer-Marcotty *et al*., 2010). It is however these facial features which are of particular interest when researching outcomes of cleft patients. Advances in 3D motion capture, using the Di4D system (Dimensional Imaging Ltd., Glasgow), have been shown its accuracy in collating volumetric, surface and shape data in 4D (Shujaat *et al*., 2014; Ju *et al*., 2016; Hallac *et al*., 2017; Lowney *et al*., 2018). Previous studies have demonstrated asymmetry in paediatric UCLP patients using static 3D images (Bugaighis *et al*., 2010; Bell *et al*., 2014). However, during function, the nasolabial area is rarely static and remains a vital complex for function and verbal / non-verbal facial

expression. Research with paediatric cleft patients has explored dynamic facial asymmetry using 3D motion capture (Hallac *et al*., 2017; Gattani *et al*., 2020). These studies are based predominately on children, however the majority of cleft patients will go on to have hard tissue / soft tissue surgery, once facial growth has ceased, in order to correct any residual facial deformities. This study aims to investigate a reproducible dynamic facial expression, maximum smile, of adult cleft patients after the completion of their cleft treatment, compared to a non-cleft group of patients.

CHAPTER 2

AIMS & NULL HYPOTHESIS

2.1 Aims

The aim of this study was to determine if the dynamic movement of the naso-labial region was similar between cleft adult patients, at the end of their treatment journey, and an age and gender matched control group.

For the purpose of this study, the naso-labial region was grossly simplified to three landmark pairs representing three important anatomical sites – the commissures of the mouth (left and right cheilion), the philtrum of the upper lip (right and left christa philtri and the nasal base (right and left alar base).

Primary outcome measure

1. The difference in maximum displacement (Euclidian distance) of left and right cheilion (commissures of the mouth) between the cleft and non-cleft groups at maximum smile.

Secondary outcome measures include:

1. For symmetry, the paired landmarks either side of the clinical midline, should move the same amount in the x, y and z direction within the same individual. Differences would indicate a level of asymmetry. Therefore the mean differences in displacement, between the three landmark pairs, were assessed in the x, y and z directions between the two groups at maximum smile.
2. The difference in the path of motion (trajectory) of the three landmark pairs between the two groups at maximum smile.

3. Asymmetry score based on the clinical midline - differences in the shape of the mouth and / or nose when it is mirrored, around the clinical midline, onto itself at maximum smile.
4. Procrustes asymmetry score – differences in the shape of the mouth and / or nose when it is mirrored onto itself trying to achieve the best fit between the two groups at maximum smile.

2.2 Null hypotheses

There is no statistical difference in magnitude of displacement (Euclidian distance) of right and left cheilion between the two groups at maximum smile.

In addition, the secondary outcome measures will be reported.

CHAPTER 3

MATERIALS & METHODS

3.1 Design

This was a case-controlled study assessing the dynamic lip function of adult patients with a repaired unilateral cleft lip ± palate at the end of their treatment journey, and comparing the outcome to previously collated data of a non-cleft control group.

3.2 Ethics

Ethical approval was requested and granted by North West - Preston Research Ethics Committee (REC reference number 16/NW/0594). Sponsorship was granted by the University of Birmingham.

3.3 Location

The study was a single centre study. Patients were recruited from the Queen Elizabeth Hospital, Birmingham, United Kingdom. Three-dimensional (3D) facial motion capture of the non-cleft control group (volunteers) had previously taken place at Leeds Dental Hospital, Leeds, United Kingdom. Three-dimensional facial motion capture of the adult patients with repaired unilateral cleft lip ± palate were taken at the Birmingham Dental Hospital, Birmingham, United Kingdom, as this was the location of the imaging system.

3.4 Sample size calculation

Sample size calculations determined a minimum sample of 12 adult patients with a repaired unilateral cleft lip ± palate was required, with a significance level of 0.05, to show a 3mm difference between the treated cleft patients and healthy control group. Jones *et al*. (2007) deemed that a difference of 3mm was clinically significant when considering landmark locations. The expected standard deviation was 2.8mm (Lowney *et al*., 2018).

3.5 Study participants

Thirteen participants attending the multidisciplinary adult cleft clinic or retainer review clinic at Queen Elizabeth Hospital, Birmingham were recruited from September 2018 to August 2019. Adults, who fulfilled the inclusion criteria, were invited to voluntarily participate in the study by letter (Appendix 8.1). Each subject was assessed by a trained clinician.

3.5.1 Inclusion criteria

The inclusion criteria for the study were as follows, patients who

- Were between 18-40 years of age.
- Had surgical repair of their unilateral cleft lip ± palate repair carried out by the Cleft Team at the Queen Elizabeth Hospital, Birmingham.
- Completed their planned orthodontic treatment and hard tissue +/- soft tissue surgery and were not contemplating additional surgical procedures i.e. they had reached the end of their treatment journey.
- Caucasian participants
- Were willing to participate in the study.
- Spoke English as their first language.

3.5.2 Exclusion criteria

The exclusion criteria were as follows;

- Paediatric cleft lip ± palate patients.
- Bilateral cleft lip ± palate patients.
- Patients with identifiable craniofacial syndromes.
- Patients in active fixed appliance treatment.
- Patients not willing to participate in the study.
- Patients requesting additional surgical procedures.

3.6 Recruitment

3.6.1 Cleft Group

Once identified by researchers, patients were informed of the study in person, or sent details of the study and invited to participate (Appendix 8.1). Following consent to be contacted, patients who were interested in participating, were sent a patient information leaflet (Appendix 8.2) with further details about the study.

Researcher YP confirmed with clinical notes and verbally with patients that they fit the inclusion criteria. Once this had been confirmed, patients were contacted to arrange an appointment to have the imaging carried out and a consent form was completed (Appendix 8.3). 3D motion capture of the adult cleft lip ± palate patients took place at the Birmingham Dental Hospital, and took approximately 20 minutes to capture and part-process the video sequence.

3.6.2 Control group

The control group was made up of non-cleft individuals who had been previously imaged using the same protocol (Lowney *et al*., 2018). The group consisted of 54 males and 54 female volunteers who were imaged whilst performing a maximum smile using the same imaging system.

3.7 Patient Imaging Equipment

3.7.1 The Di4D motion capture system

The Di4D™ Pro passive stereophotogrammetric capture system (Dimensional Imaging Ltd., Glasgow, Scotland, U.K.) was used. Di4D™ Pro uses digital video cameras to capture sequences of high resolution, colour 3D facial images. The system was made up of two "pods" of cameras, each comprised of three video cameras: one colour and two monochrome (Model avA 1600-65km/kc, Kodak sensor model KAI-02050, Basler, Germany). The cameras were synchronised, at a capture rate of 60 frames per second with a resolution of 2048 x 2048 pixels. Two LED studio lights (NanGuang CN-600 HS Studio LED Lighting, China) were used alongside the camera pods to provide the appropriate light source for video capture. The software uses blue screen subtraction to separate the facial image into the foreground whilst subtracting the background. Therefore the participant was imaged whilst sitting in front of a blue background, Figure 3.1.

Each camera pod (three video cameras) was connected to its own PC, running Microsoft Windows 10. The two PC's were hard-wired together for image capture and processing. Each PC used StreamPix software (Norpix) to capture the three video

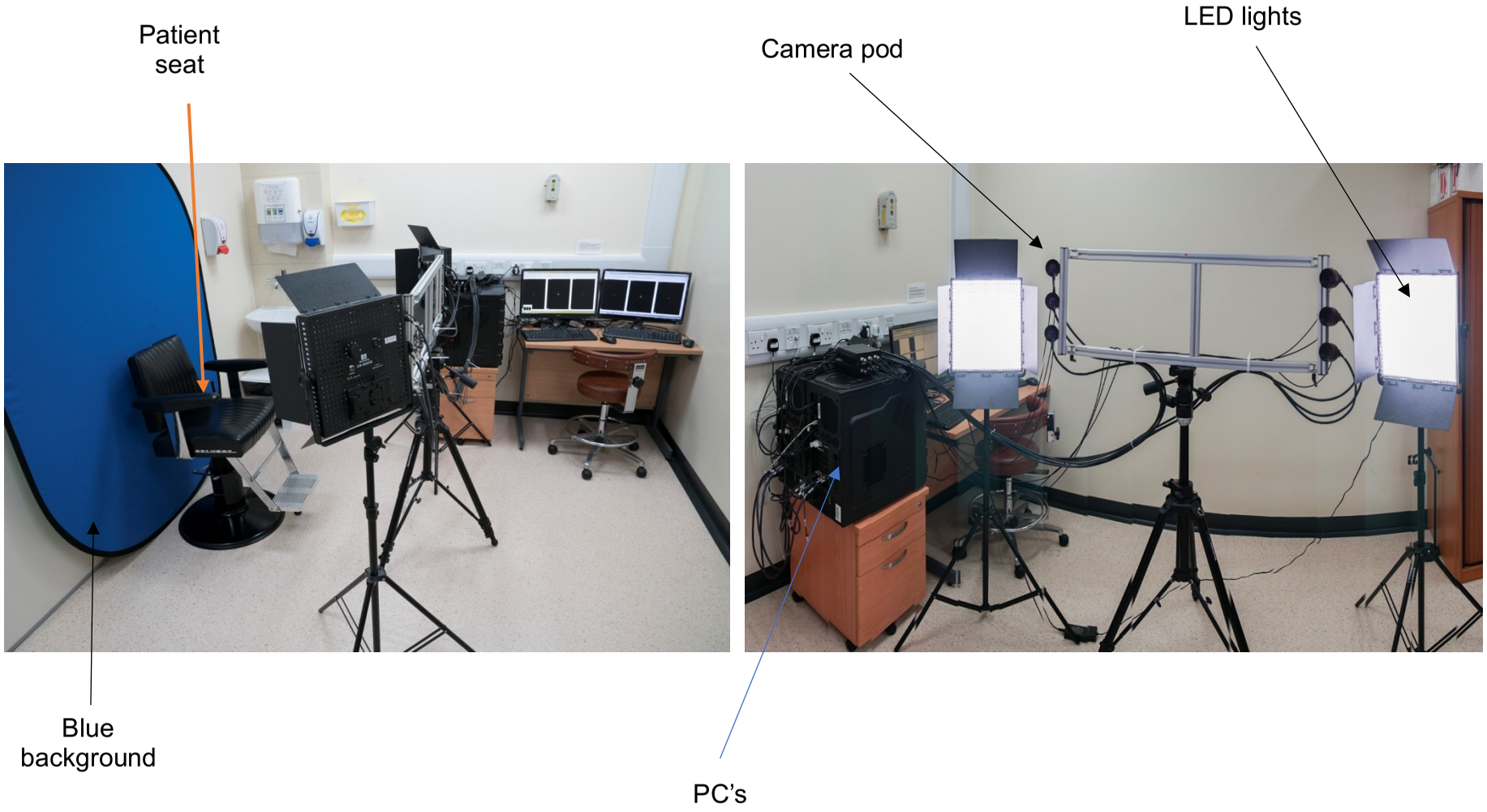


Figure 3.1 Di4D stereophotogrammetry imaging system (Di4D Pro)

streams from each pod. On one PC StreamPix Remote (Norpix) software ensured the two pods (six video cameras) were synchronised to all start, capture at the same frame rate and stop at exactly the same time. For each pod, the three video stream cameras were immediately saved to a Solid State Drive (SSD) for future processing in proprietary .SQE format.

3.7.2 Calibration of Di4D system

Prior to image capture, calibration of the camera system was necessary to determine the internal and external camera parameters. This process determines each of the camera's focal lengths, intrinsic parameters and their orientation in relation to each other. A calibration target, supplied with the 3D imaging system, was used to calibrate the system, Figure 3.2. The calibration target was placed 135cm from the camera pods in a position where all six cameras could see the same region on the calibration target. Using Streampix Remote a static image of the target was taken, in fact six images of the target were taken simultaneously. The calibration target was repositioned at a different angle and the process repeated; this was repeated six times in total with the target in a different position. As a result, 36 individual images of calibration target were taken and saved.

For processing, the 36 images (six captures stored on six different SSD's) were all saved to one of the PC's in a common folder. Using DiHydra software (Dimensional Imaging Ltd., Glasgow, Scotland, U.K.) all the necessary software parameters were adjusted and the calibration target images were uploaded and processed by DiHydra to produce a calibration file for that session. This calibration file was saved and would

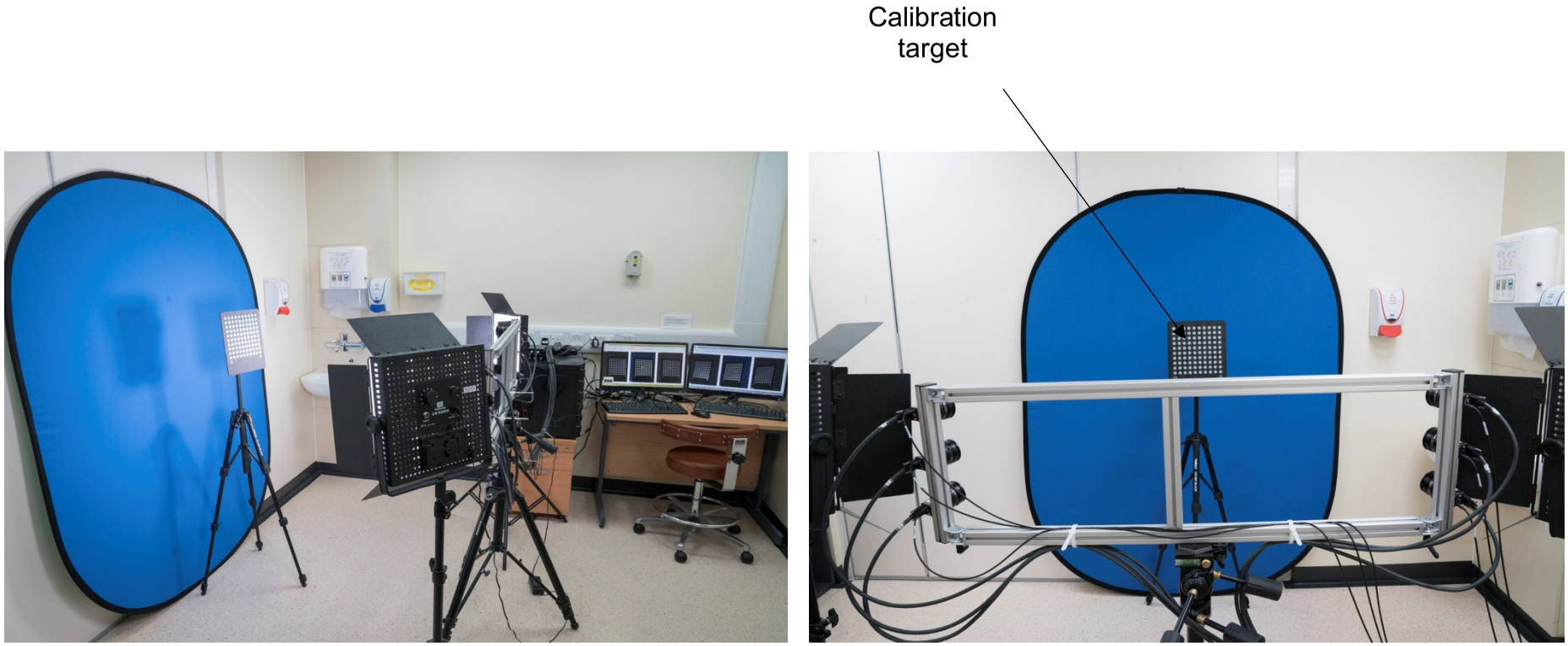


Figure 3.2 Di4D Imaging system - calibration target in place

be combined with the participant video sequence to create a 3D motion capture sequence.

3.8 Imaging of patients

Prior to image capture, patients were trained by the researcher (YP) to perform a maximum lips apart smile from rest, with teeth in maximum intercuspation. The facial expression was demonstrated several times and patients were asked to repeat it until they were comfortable performing the facial expression. Patients were then seated in front of the blue screen and camera system and asked to remove any glasses to prevent reflection of light. Loose hair strands over the face had the potential to disrupt the video captures, therefore surgical caps were provided, if required, to hold any hair away from the forehead. The height of the participant was adjusted making sure the patient was correctly positioned relative to the two camera pods within the StreamPix live preview software. Patients were asked to focus on a red marker, placed in the middle of the camera rig framework.

Once the correct head position was achieved, and the patient had confirmed they were ready to start, capturing began, using the “record” function in StreamPix Remote. As with calibration, StreamPix remote synchronised all the cameras. The recording was started prior to the smile i.e. at rest and stopped beyond maximum smile being achieved. The video sequence was saved in propriety .SQE format. Prior to discharging the participant, the video capture sequence was reviewed, using the playback function in StreamPix to ensure there were no obvious errors. If the maximum smile expression was deemed to be erroneous due to head positioning or smile

expression, the file was discarded and the recording was repeated. Once the participant had left, the video sequence was viewed again in StreamPix and the frame number at which the smile expression started (rest frame) and the frame at which point maximum smile (maximum frame) was reached were noted.

The six video sequences captured for each participant were stored on the six individual SSD's, three sequences per PC. The video captures from all six cameras were copied into one folder (sessions folder) on one PC for each subject. DiHydra was used to build the 3D facial sequence by loading the six video sequences together with the calibration file for that session. This process created a series of 3D images (60 3D images per one second of video capture at 60 fps). The 3D video sequence was saved and could be viewed as a continuous video sequence using Di4Dview or each 3D image / frame could be viewed individually using Di3Dview. The total file size for each 3D video sequence was around 10GB.

3.9 Pre-analysis image processing

This process involved four stages, the first stage was to re-orientate the first image of each sequence into a standardised "clinical" position – this is termed the "anchor frame". The second stage was to re-orient the remaining frames of the capture or sequence to the anchor frame. The third stage involved landmarking for automatic tracking, and the final stage was landmark placement and mesh conformation for mesh tracking.

3.9.1 Stage 1 – Anchor frame re-orientation

For each individual, the first image of their sequence was loaded into Di3Dview and the image was re-orientated relative to the "principle places" – the x, y and z planes, Figure 3.3 and Figure 3.4. The x axis (x-z plane) was parallel to the inter-pupillary line and the Frankfort plane, the y axis (y-z plane) was set to pass through the mid-facial axis at soft tissue Nasion and was perpendicular to the x-z plane. Finally, the z axis (x-y plane) was set to pass though right and left tragus, Figure 3.5. The image was viewed by two experienced clinicians to ensure the patient was "clinically correct" i.e. as if they were being viewed during a clinical assessment. This re-orientated frame was saved as the "anchor frame".

3.9.2 Stage 2 – Capture sequence re-orientation

The translation and rotation matrix that was need to re-orientate the anchor frame was then applied to all the remaining images in the subject "session" folder, which re-oriented each of the frames in the sequence in the same orientation to the principle planes.

3.9.3 Stage 3 – Landmark tracking

For each participant the 3D capture sequence was imported into Di4Dview. Seventeen facial landmarks were digitally placed on the first frame, Table 3.1 and Figure 3.6. Using Di4Dview it was possible to view the image in three different views simultaneously, zooming in and rotating the image to accurately and correctly place each landmark in all three dimensions. Four "stabilisation landmarks" were placed on

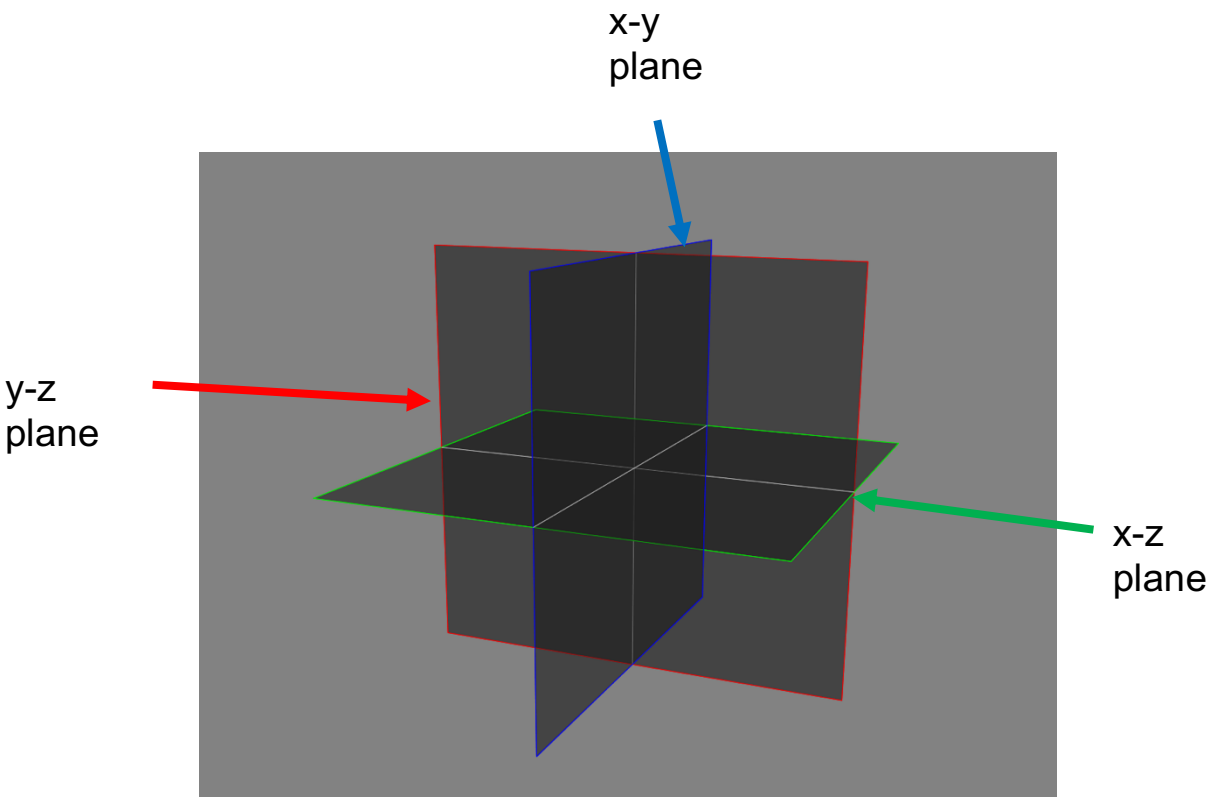


Figure 3.3 Principle planes used for image reorientation

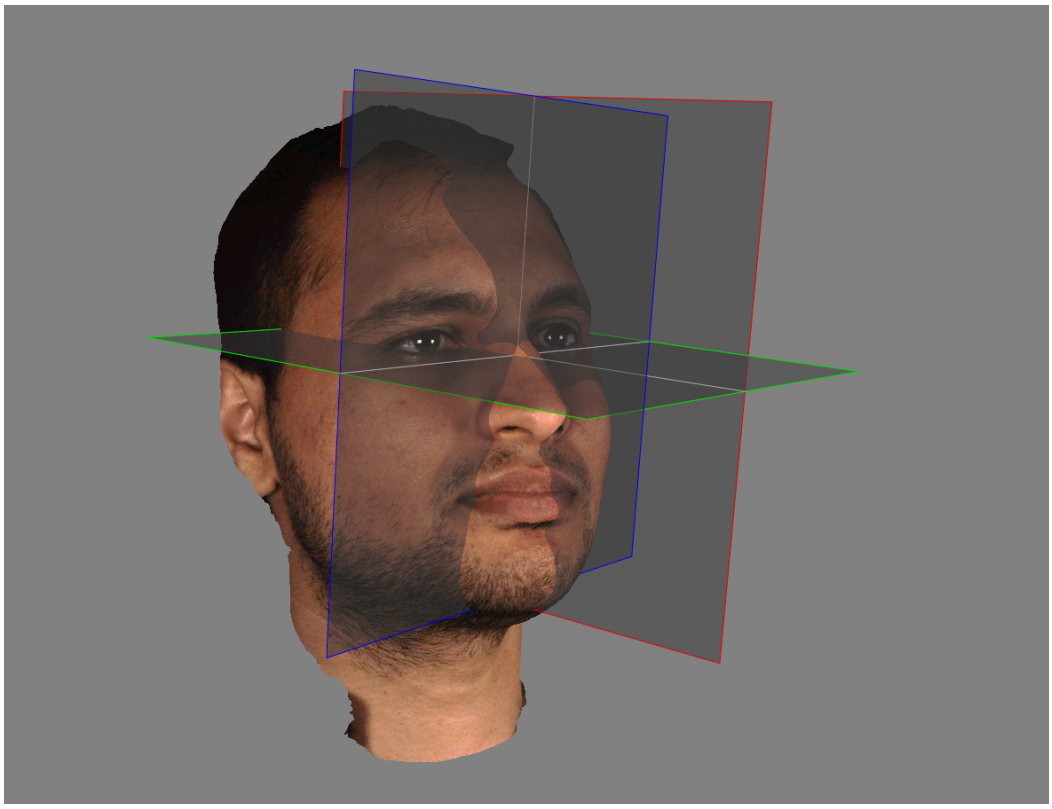


Figure 3.4 Image not aligned to principle planes

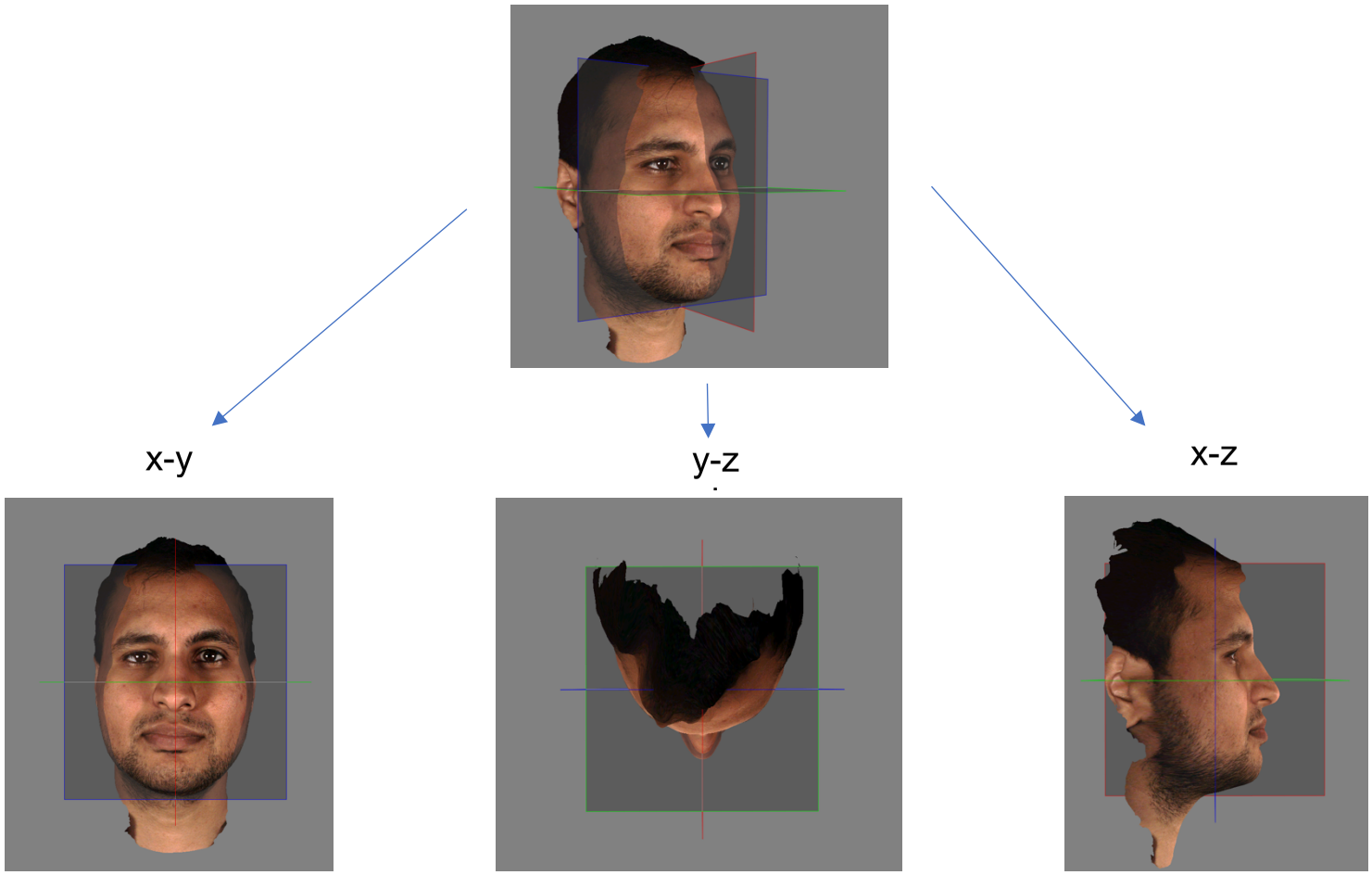


Figure 3.5 Image reoriented to principle planes and clinical assessment

Landmark number	Landmark name	Landmark definition
1 - 4		Points used for head stabilisation.
5 and 11	Cheilion	Points located at each labial commissure.
6 and 10		Points located on the vermilion border midway between cheilion and christa philtre.
7 and 9	Christa philtre	Points on the crest of the philtrum, located just above the vermilion border.
8	Labrale superius	Point indicating the midpoint of the upper vermilion border.
12 and 14		Points midway between cheilion and labrale inferius.
13	Labrale inferius	Point indicating the lower border of the lower lip.
15 and 16	Subalare	Point on the margin of the base of the ala where it disappears into the skin of the upper lip.
17	Pronasale	Most prominent point on nose tip selected where normal is perpendicular to frontal plane in profile view

Table 3.1 Landmark definitions used for tracking



Figure 3.6 Seventeen landmarks used for tracking – 3 different views

the forehead to control any head movement that may have occurred during the facial expression.

Once the first frame of each subject was landmarked, the automatic tracking function within the Di4Dview software was enabled to track each of the landmarks for all the frames of that sequence. With this functionality, each landmark can be tracked throughout the whole video sequence, using the process of “optical flow” in all three planes (x, y and z), automatically. The accuracy of this process has previously been reported and was found to be around 0.5mm (Al-Anezi *et al*., 2013), Figure 3.7

Following automatic tracking of the landmarks, x, y and z co-ordinates of each landmark per frame were exported from the Di4Dview software in a “.pc2” format. The .pc2 file contained the x, y and z co-ordinates for every one of the tracked landmarks for each of the frames. At 60 frames per second, and 17 landmarks per frame this produced 1020 landmark co-ordinates per second of sequence. These were then saved for later analysis.

3.9.4 Stage 4 – Mesh tracking

For each patient the anchor frame was loaded into Di3Dview together with a generic mesh, Figure 3.8. The generic mesh was a computer-generated symmetrical face with a known number of vertices i.e. 3076. The conformation process produces a facial mesh which has then same surface topography as the original facial image i.e. it looks the same but is made up a standardised number of vertices, in this case 3076. The additional benefit is that there is anatomical correspondence between images.



Figure 3.7 Tracked smile showing rest (A), ½ median frame (B), median frame (C), ¾ median frame (D) and maximum smile (E)



Figure 3.8 Generic mesh and first frame ready for conformation

For example, vertex number 567 may represent Pronasale, therefore vertex 567 will represent Pronasale across all images for the same patient and also between patients. This allows direct comparison of landmarks without needing to place all 3076 landmarks, as each vertex acts as a landmark.

Twenty-two landmarks were placed on the anchor frame for conformation, the same 22 landmarks were placed on the generic mesh, Table 3.2 and Figure 3.9 and Figure 3.10. Using the “Shape transfer” feature in DI3Dview, the generic mesh was elastically deformed to the morphology of the anchor frame mesh whilst constraining the mesh at the 22 landmarks. The conformed generic mesh was then saved in Wavefront (.OBJ) format, Figure 3.11 and Figure 3.12.

For each participant their conformed generic mesh was loaded into DI4Dview together with their 3D sequence, Figure 3.13. Using the “Mesh tracking” function in DI4Dview the vertices of the conformed generic were transferred as landmarks to the first frame of the sequence. These were then automatically tracked as before. In this way, the manually placed 22 landmarks become 3076 quasi-landmarks in a semi-automated process. This also resulted in dynamic movement of the conformed generic mesh which reflected the movement of the 3076 transferred to the 3D sequence. It was then possible to export each frame of the 3D sequence as the conformed generic mesh equivalent in Wavefront (.OBJ) format, Figure 3.14.

Landmark number	Landmark name	Landmark definition
1 and 2	Exocanthion	Point on the outer commissure of the eye fissure.
3 and 4	Endocanthion	Point on the inner commissure of the eye fissure.
5 and 11	Cheilion	Points located at each labial commissure.
6 and 10		Points located on the vermilion border midway between cheilion and christa philtre.
7 and 9	Christa philtre	Points on the crest of the philtrum, located just above the vermilion border.
8	Labrale superius	Point indicating the midpoint of the upper vermilion border.
12 and 14		Points midway between cheilion and labrale inferius.
13	Labrale inferius	Point indicating the lower border of the lower lip.
15 and 16	Subalare	Point on the margin of the base of the ala where it disappears into the skin of the upper lip.
17	Pronasale	Most prominent point on nose tip selected where normal is perpendicular to frontal plane in profile view
18	Subnasale	Midpoint of columella, maximum concavity at junction of lip skin and columella
19	Nasion	Point in the midline of the both the nasal root and the nasofrontal suture, always above the line that connects the two inner canthi.
20	Glabella	Most prominent point between the eyebrows, in the midline
21 and 22	Tragus	Midoint of medial margin of the facial insertion ofd the tragus
23	Menton	Lowest point on chin curvature
24	Pogonion	Most anterior point in midline of chin, marked with normal perpendicular to frontal plane in profile view

Table 3.2 Landmark definitions used for conformation

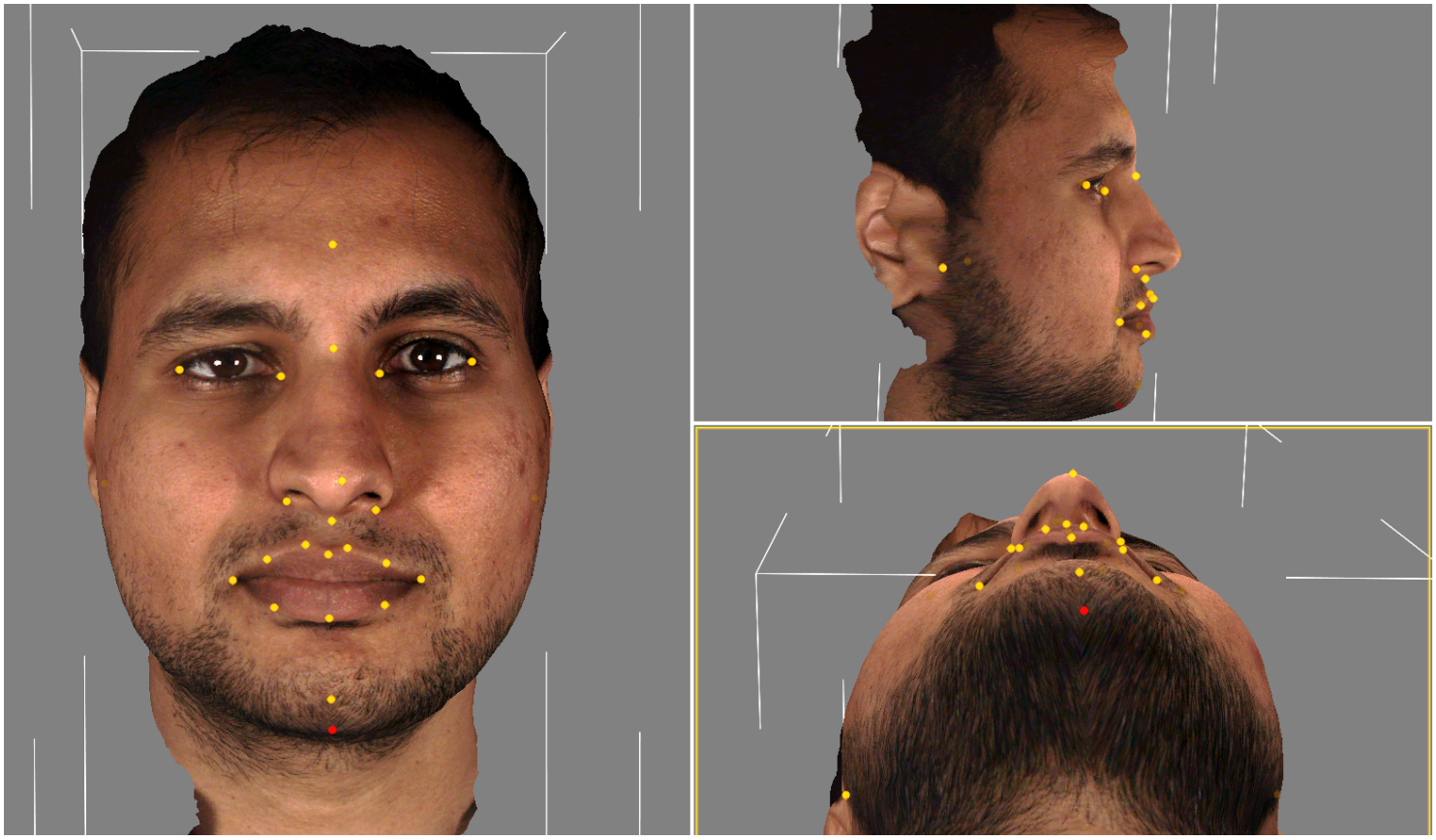


Figure 3.9 Twenty-four landmarks used for conformation – 3 different views



Figure 3.10 Twenty-four landmarks placed on both the generic mesh & anchor frame

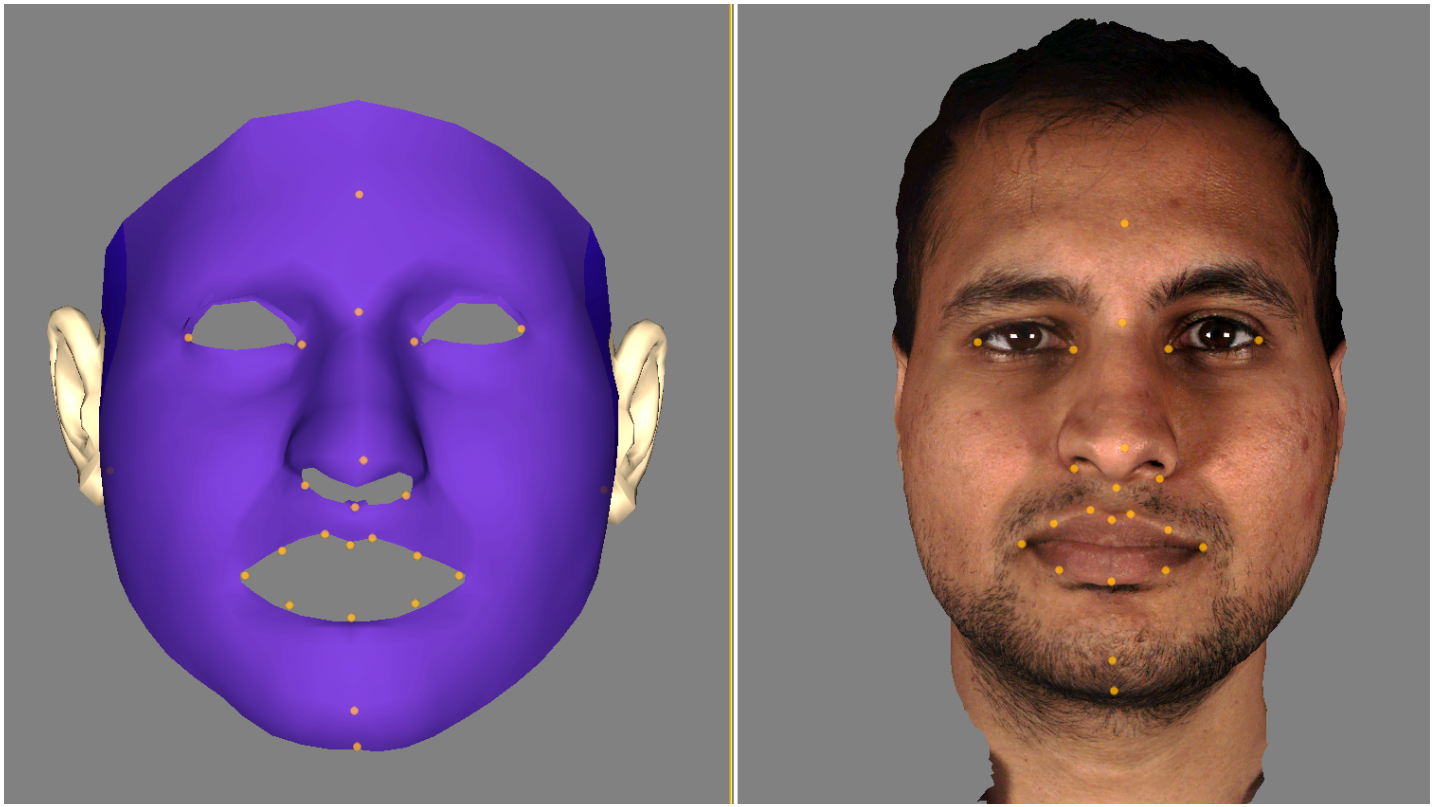


Figure 3.11 Conformed generic mesh

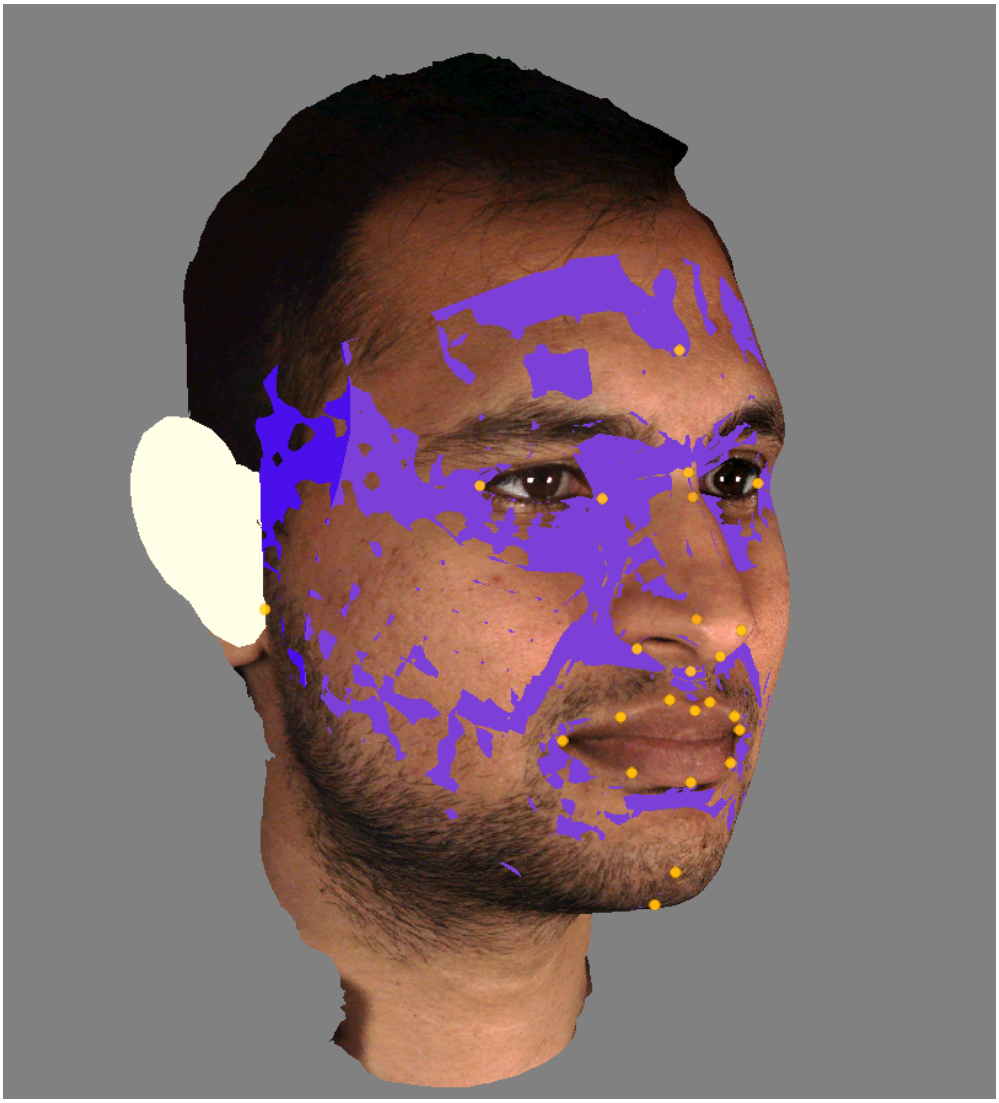


Figure 3.12 Conformed generic mesh superimposed over anchor frame to show closeness of fit

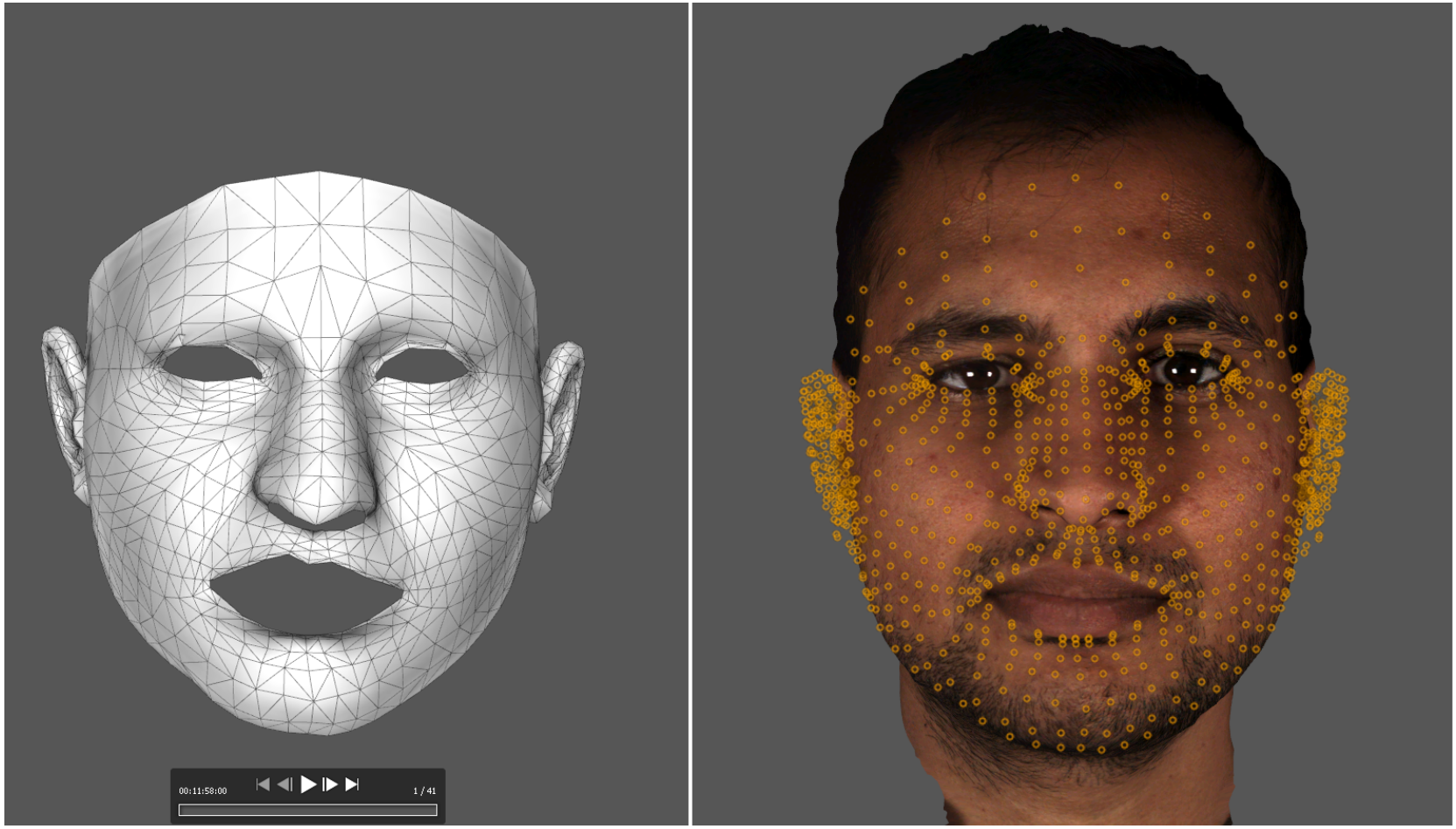


Figure 3.13 Generic mesh landmarks (vertices) transferred to original mesh for tracking

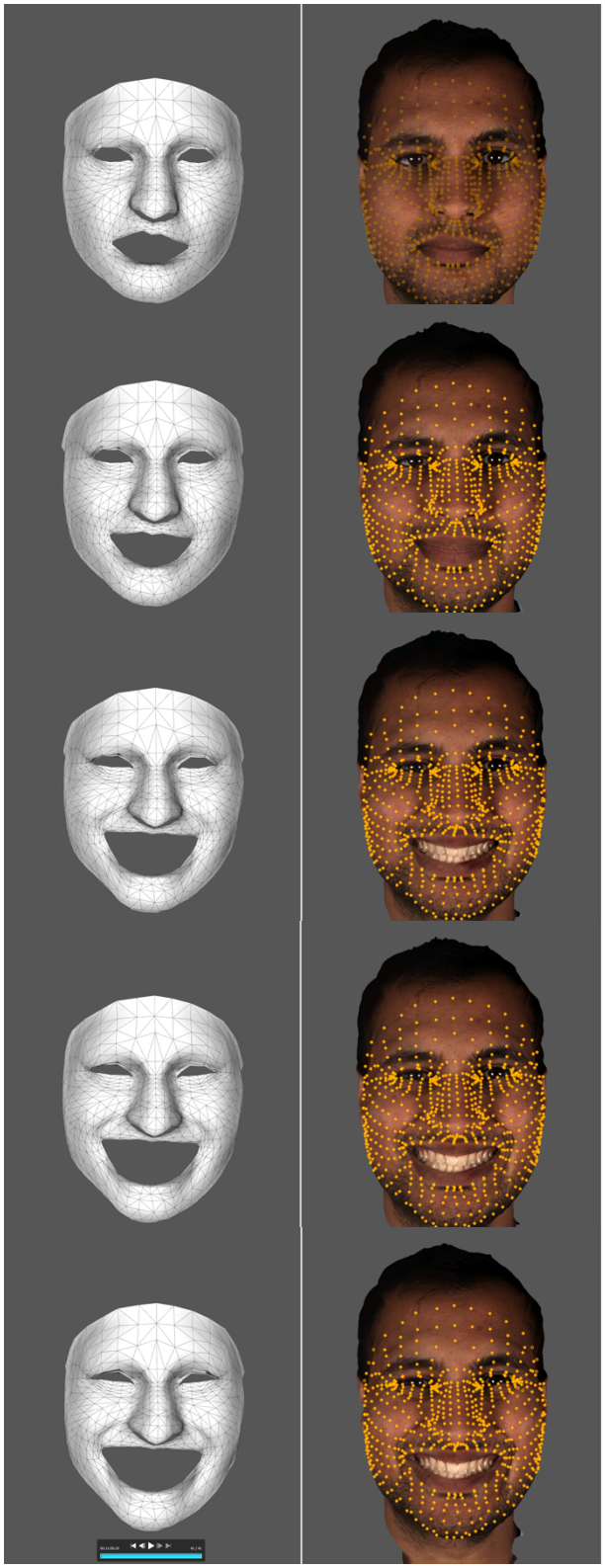


Figure 3.14 Mesh tracked smile showing rest (A), ½ median frame (B), median frame (C), ¾ median frame (D) and maximum smile (E)

3.10 Analysis

Defining which attributes are necessary to determine a smile as clinically symmetrical are not well listed in the literature. They would need to include the following:

1. Bilateral structures either side of the clinical midline should displace an equal amount i.e. the magnitudes should be equal. To be more specific, the displacement of the structures in the x, y and z direction should be the same rather than just the Euclidian distance.
2. The path or trajectory that bilateral structures follow during displacement, should be the same either side of the clinical midline.
3. The speed of displacement of bilateral structures either side of the clinical midline should be equal.
4. The shape of the mouth and / or nose should be the same when it is mirrored onto itself around the clinical midline – “Clinical midline asymmetry score”.
5. The shape of the mouth and / or nose should be the same when it is mirrored onto itself trying to achieve the best fit – “Procrustes asymmetry score”.

Landmark tracking was used to test points 1 & 2 whilst Mesh tracking was using test points 4 and 5. Point 3, the speed was not investigated in this study, as this could not be easily standardised.

3.10.1 Landmark displacement analysis

In-house developed MATLAB software (MATLAB and Statistics Toolbox Release 2017b, The Math-Works, Inc., Natick, Massachusetts, USA) was used to determine the displacement of landmark pairs from rest to maximum smile. For each landmark,

the x, y and z co-ordinates at rest were subtracted from the x, y and z co-ordinates of the next frame; this was repeated for all the remaining frames in the sequence. This indicted how much the landmarks had moved from rest, in the x, y and z direction, in each frame. This also allowed calculation of the Euclidian distances. The landmark pairs were the corners of the mouth – right and left cheilion (LM5 and LM11), philtrum of the lip – right and left cristae philtre (LM7 and LM9) and right and left alar bases (LM15 and LM16).

The data was tested for normality and was found to be normality distributed. The maximum displacement of each landmark pair, in the x, y, z direction and Euclidian distance, were compared between the UCLP group and the control group, using a two-sample *t*-test. The signed and absolute differences between the displacements of landmarks pairs within the control group and the cleft group were calculated. For symmetry, when comparing bilateral landmark pairs within each group, the difference between displacements should be as close to zero as possible.

3.10.2 Landmark path during motion - Fréchet distance

If a graph of landmark displacement, for example for right and left cheilion, is plotted against time for an individual and superimposed at time = 0; then the distance between the two curves should be zero if the trajectory of the two landmarks are identical. The greater the distance between the two curves (Fréchet distance), the greater the difference in trajectory of the two landmarks and the more asymmetric the movement.

Using in-house developed MATLAB code, the Fréchet distance each landmark moved in the x, y, z direction was calculated. This involved firstly adjusting for the time taken for each landmark in the pair to go from rest to maximum smile. Ideally, the two landmarks should have moved the same distance over the same time period. This will not always be the case, so the time taken to reach the maximum point needed to be compressed or dilated so both landmark displacements were on a common time line, this process is referred to as “dynamic time warping”. This was carried out prior to calculating the Fréchet distance. The Fréchet distance in the x, y, z direction was calculated for each individual in the UCLP group and the control group.

3.10.3 Mesh tracking - Clinical midline asymmetry score

For each participant the “at rest” conformed generic mesh in .OBJ format was loaded into MATLAB and using an in-house developed code the vertices (or landmarks) making up the mouth periphery were identified, Figure 3.15. These landmarks were then reflected around the clinical midline; with perfect symmetry in position and shape, the original lip landmark configuration should lie over their mirrored landmark configuration. The distance between the two landmark sets would be zero and the asymmetry score would be zero. The greater the difference in the two landmark configurations the greater the degree of asymmetry and the higher the asymmetry score. This was repeated for the maximum frame and the median frame. In total, three asymmetry scores were produced per individual. This was repeated for the landmarks demarcating the nasal rim.

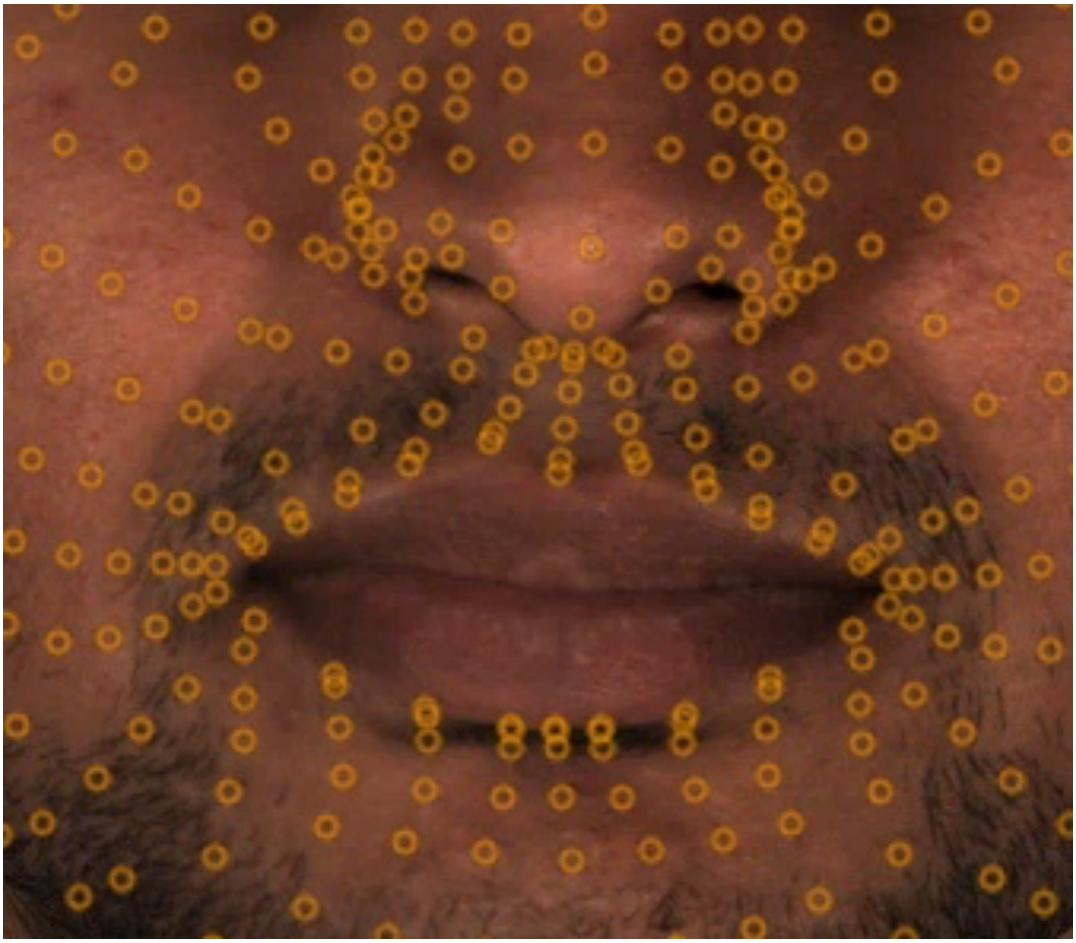


Figure 3.15 Landmarks (vertices) extracted from around the naso-labial complex

3.10.4 Mesh tracking - Procrustes midline asymmetry score

For each participant the “at rest” conformed generic mesh in .OBJ format was loaded into MATLAB and using an in-house developed code, the vertices (or landmarks) making up the mouth periphery were identified. These landmarks were then aligned using partial Procrustes superimposition, which involved reflection, translation and rotation but no scaling of the mirrored landmark configuration. Again, based on the above, three asymmetry scores were produced per individual – rest frame, median frame and the maximum frame. This was repeated for the landmarks demarcating the nasal rim at the same three time points.

CHAPTER 4

RESULTS

4.1 Commissures of the mouth

4.1.1 Maximum displacement of right (LM5 non-cleft) and left (LM11 cleft) cheilion between the control and cleft groups

For the cleft group, maximum displacement of LM5 and LM11, in the x, y, z direction and Euclidian distance were statistically significantly ($p<0.05$) less compared to the control group during maximum smile. The displacement of both LM5 and LM11, in the x, y, z direction and Euclidian distance, was between 20 - 40% less in the cleft group compared to the control group, Table 4.1. The mean differences in Euclidian distances in LM5 and LM11, between the two groups, were greater than 3mm and would therefore be deemed clinically significant. For all the measurements the 95% confidence intervals for the differences were close to or exceeded the 3mm clinically significant threshold.

For symmetry, the mean absolute difference in displacement between LM5 and LM11 within the same individual, should be as close to zero as possible. In the cleft group, the difference ranged from 1.0 to 2.0mm, whilst in the control group ranged 0.7mm to 0.9mm, Table 4.2.

Table 4.1 Maximum displacement of right (LM5 non-cleft) and left (LM11 cleft) cheilion for the control and the cleft groups

	x-direction		y-direction		z-direction		Euclidian distance	
	LM5	LM11	LM5	LM11	LM5	LM11	LM5	LM11
Control								
Mean (mm)	9.6	9.7	10.5	9.9	11.5	12.1	18.5	18.6
SD (mm)	2.2	2.2	2.7	2.4	2.3	2.8	2.6	3.0
Cleft								
Mean (mm)	7.3	5.9	8.0	7.8	7.6	7.4	13.5	12.5
SD (mm)	2.4	1.6	2.4	2.2	2.1	2.8	3.0	2.9
Differences								
Mean difference (mm)	2.3	3.8	2.5	2.2	3.9	4.7	5.1	6.1
Lower 95% CI for the difference (mm)	0.4	2.2	0.5	0.3	2.2	2.4	2.8	3.7
Upper 95% CI for the difference (mm)	4.1	5.3	4.5	4.0	5.7	6.9	7.3	8.6
p-value	**0.017**	**0.001**	**0.018**	**0.024**	**0.001**	**0.001**	**0.001**	**0.001**

Table 4.2 Differences between right (LM5 non-cleft) and left (LM11 cleft) cheilion displacement within the control and cleft groups

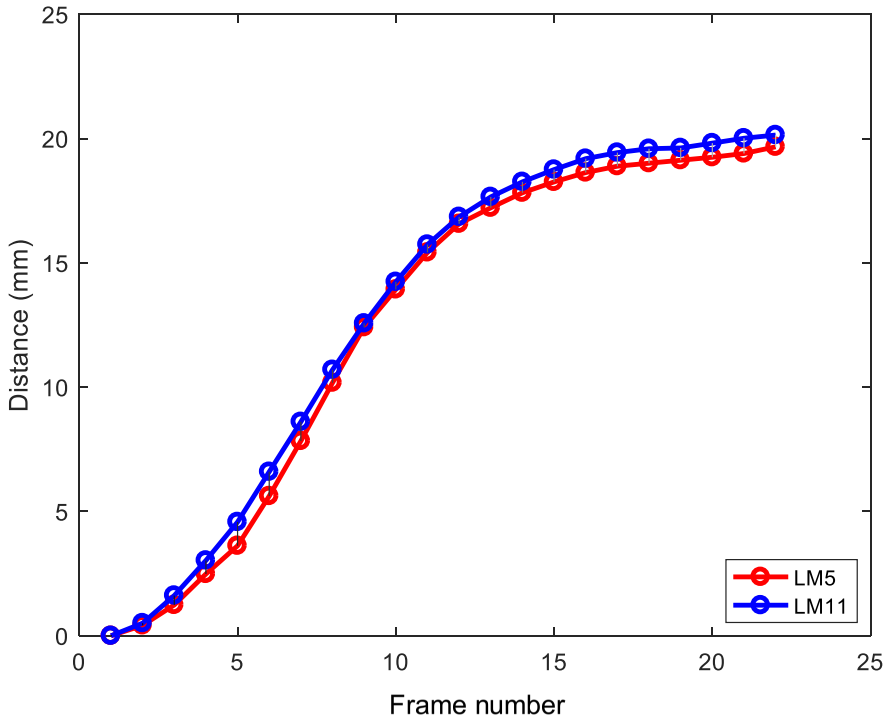
	Difference between LM5 & LM11							
	x-direction		y-direction		z-direction		Euclidian distance	
	Signed	Absolute	Signed	Absolute	Signed	Absolute	Signed	Absolute
Control								
Mean (mm)	-0.1	0.7	0.4	0.9	-0.4	0.8	0.0	0.9
SD (mm)	0.9	0.5	1.0	0.6	1.1	0.8	1.2	0.8
Cleft								
Mean (mm)	1.4	1.7	0.2	1.0	0.2	1.5	1.0	2.0
SD (mm)	1.7	1.3	1.3	0.8	1.8	1.0	2.4	1.6

4.1.2 Trajectory of right (LM5 non-cleft) and left (LM11 cleft) cheilion between the control and cleft groups

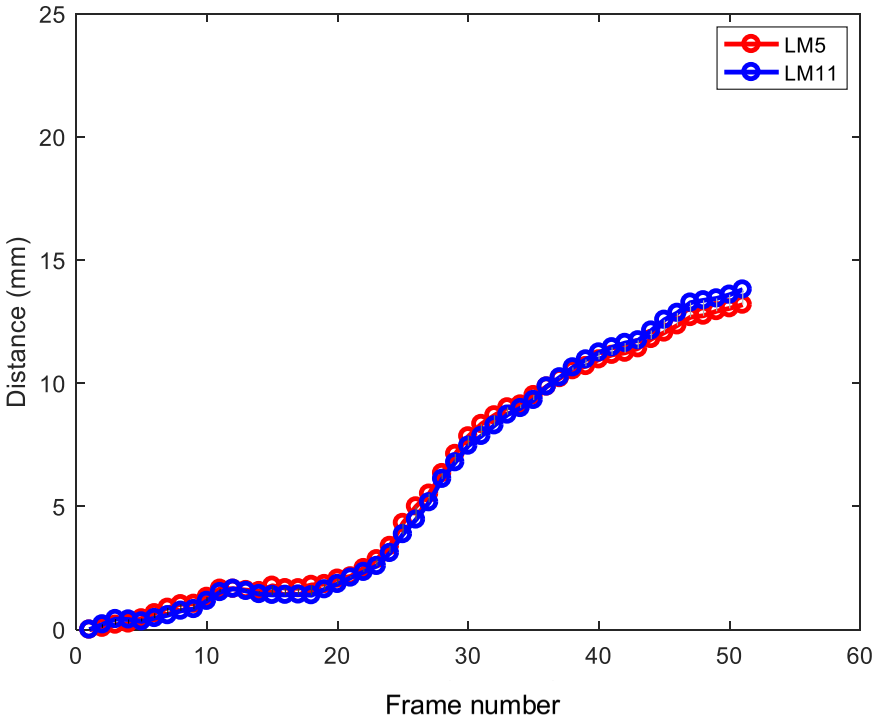
Table 4.3 shows that within the control group, right and left cheilion (LM5 and LM11) did not follow the same path or trajectory and there was a baseline level of asymmetry. An example of a plotted trajectory of right (LM5 non-cleft) and left (LM11 cleft) cheilion for a non-cleft individual and cleft individual both with the lowest and highest Fréchet distances are shown in Figure 4.1 and Figure 4.3. In the cleft group, the Fréchet distance was larger in x, y and z directions. As a frame of reference, keeping left cheilion still and only smiling moving right cheilion i.e. a marked left facial paralysis, would produce a Fréchet distance over 12.0, Figure 4.3.

Table 4.3 Trajectory of right (LM5 non-cleft) and left (LM11 cleft) cheilion for the control and cleft groups

	Control					**Cleft**			
	x	y	z	Euc		x	y	z	Euc
Mean	1.18	1.24	1.57	1.41		2.06	1.45	1.90	2.56
SD	0.32	0.43	0.80	0.40		1.14	0.78	0.97	1.27

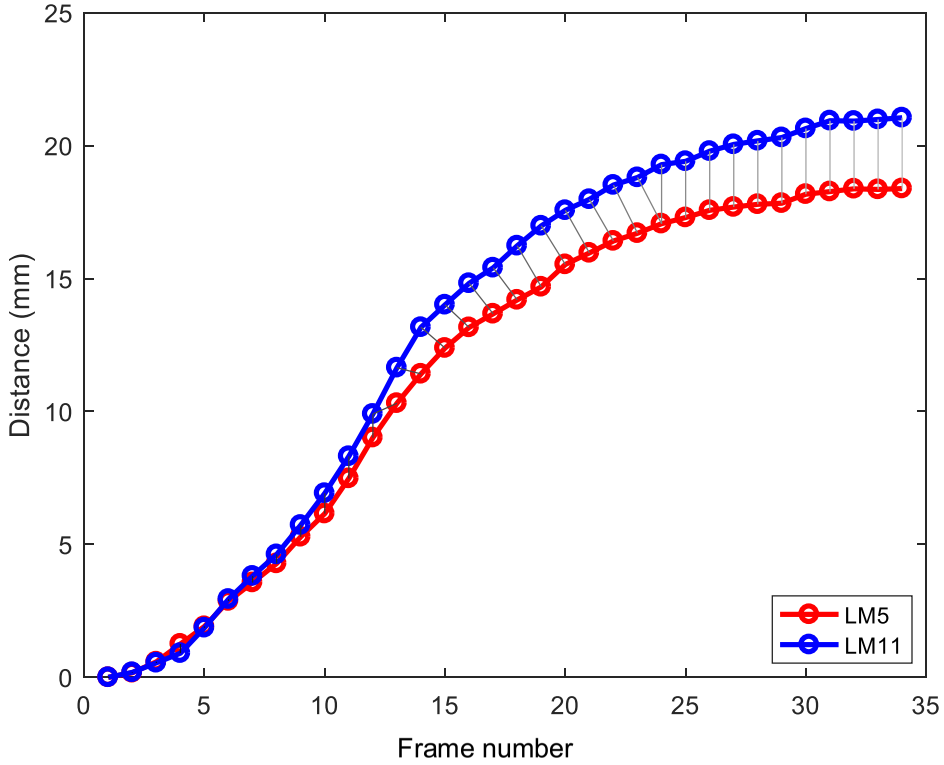


(A) Non-cleft subject
Lowest Fréchet Distance (1.0)

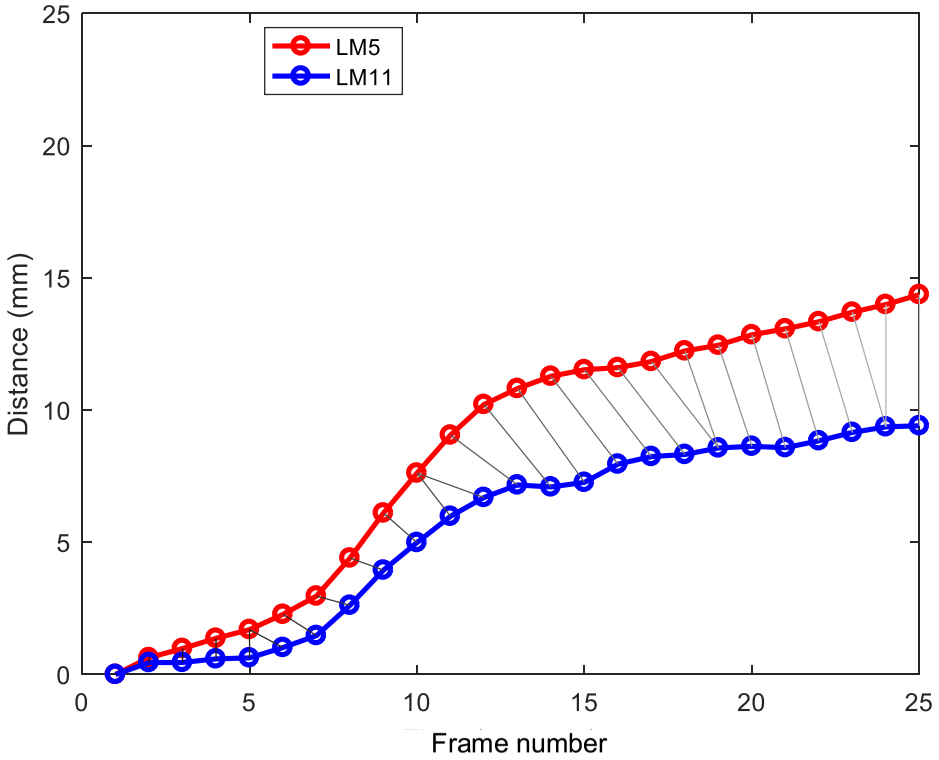


(B) Cleft subject
Lowest Fréchet Distance (0.7)

Figure 4.1 Example trajectory of right (LM5 non-cleft) and left (LM11 cleft) cheilion for a non-cleft individual (A) and cleft individual (B) both with the lowest Fréchet distances

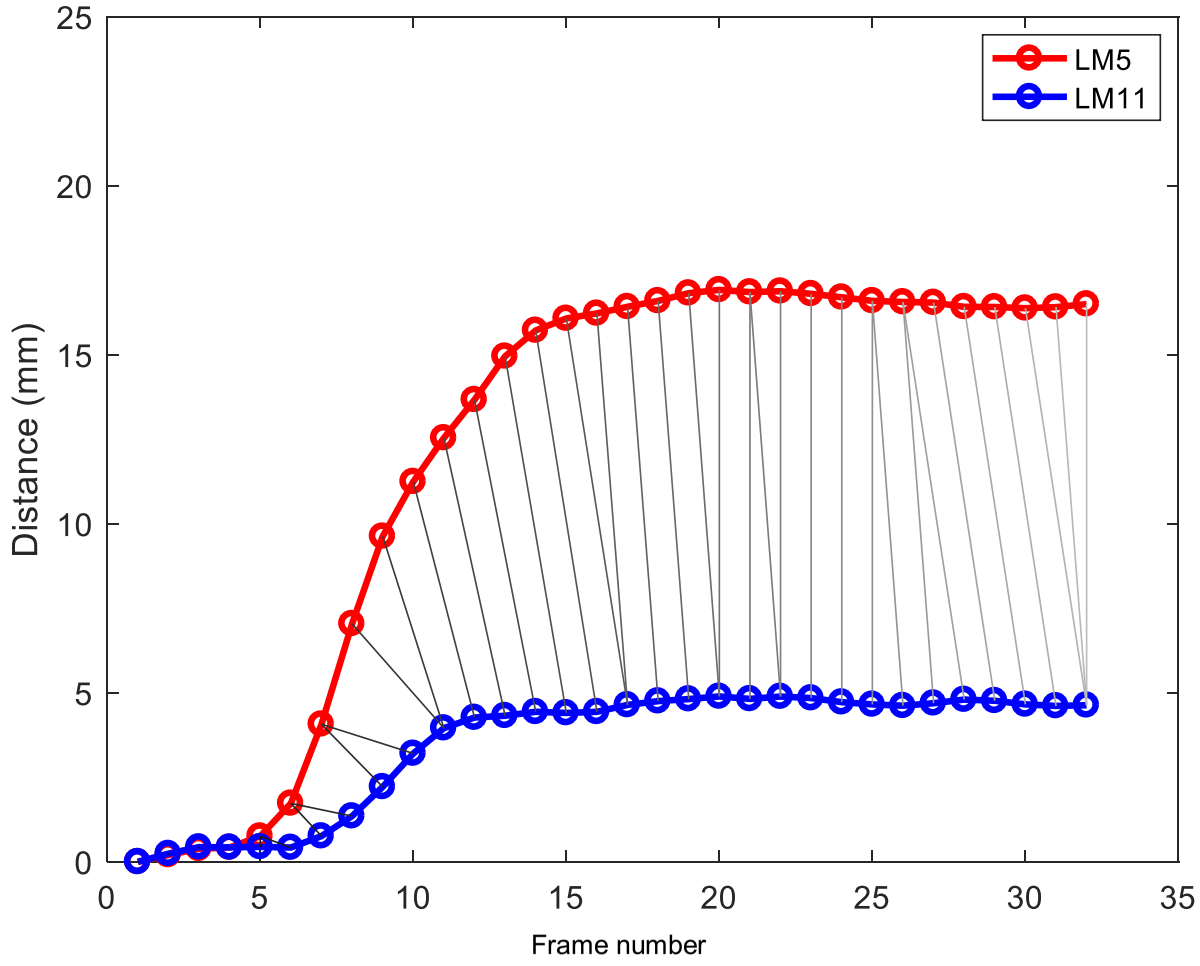


(A) Non-cleft subject
Lowest Fréchet Distance (2.7)



(B) Cleft subject
Lowest Fréchet Distance (5.0)

Figure 4.2 Example trajectory of right (LM5 non-cleft) and left (LM11 cleft) cheilion for a non-cleft individual (A) and cleft individual (B) both with the largest Fréchet distances



Bell's Palsy patient
Fréchet Distance (12.0)

Figure 4.3 Trajectory of right (LM5) and left (LM11) cheilion of a patient with Bell's Palsy and marked left facial paralysis

4.1.3 Asymmetry of the lips when smiling reflecting around the clinical midline between the control and cleft groups

When reflecting the 24 landmarks outlining the vermillion border of the lips (3D configuration), around the clinical midline; for perfect symmetry, in position and shape, the original lip 3D landmark configuration would lie exactly over the mirrored 3D landmark configuration. Any differences in distance between the original and mirrored landmark pairs would be a measure of asymmetry. The greater the score above zero, the greater the degree of asymmetry.

Table 4.4 shows that in the non-cleft control group the mean asymmetry score at rest was 1.12 ± 0.40. From rest to maximum smile, the mean asymmetry score increased to 1.55 ± 0.43. In the cleft group, the mean asymmetry score was higher at rest (1.78 ± 0.46), compared to the non-cleft control group and increased to 2.14 ± 0.80 at maximum smile. Following a two-sample t-test the differences between the two groups at each time point were statistically significant ($p<0.05$). The upper 95% confidence interval was close to 1.

Decomposing the asymmetry scores in the x, y and z directions showed that in both groups, the largest mean asymmetry score was seen in the x-direction, i.e. in a horizontal direction. The lowest mean score was in the y-direction.

4.1.4 Symmetry of the lips using Procrustes superimposition between the control group and the cleft group

When reflecting the 24 landmarks outlining the lips (3D configuration), around an arbitrary midline and then using partial General Procrustes Analysis (partial GPA), if

Table 4.4 Asymmetry score of the lips during smiling, reflecting around the clinical midline, for the control and cleft groups

		Asymmetry score		x-direction		y-direction		z-direction	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD
Cleft									
	Rest	1.78	0.46	1.18	0.58	0.58	0.29	0.81	0.47
	Median	1.96	0.70	1.38	0.72	0.65	0.39	0.80	0.38
	Maximum	2.14	0.80	1.51	0.77	0.74	0.45	0.82	0.37
Control									
	Rest	1.12	0.41	0.83	0.46	0.32	0.15	0.43	0.16
	Median	1.46	0.47	1.02	0.47	0.52	0.23	0.61	0.22
	Maximum	1.55	0.43	1.05	0.45	0.57	0.24	0.66	0.19

there was perfect symmetry in shape (effects of position have been removed), then the original lip 3D landmark configuration should lie over the mirrored 3D landmark configuration. Again, any differences in distance between the original and mirrored landmark pairs would be a measure of asymmetry. The greater the score above zero, the greater the degree of asymmetry.

Table 4.5 shows that in the non-cleft control group the mean asymmetry score was 0.65 ± 0.18 at rest. From rest to maximum smile, the asymmetry score increased to 0.99 ± 0.35. In the cleft group, the mean asymmetry score was higher at rest (0.89 ± 0.31), compared to the non-cleft control group and increased to 1.29 ± 0.44 at maximum smile. Following a two-sample t-test the differences between the two groups at rest and median smile were statistically significant ($p<0.05$). However, at maximum smile the difference was not statistically significant ($p = 0.073$).

Decomposing the asymmetry scores in the x, y and z directions showed that in both groups, the largest mean asymmetry score was seen in the x-direction, i.e. in a horizontal direction. The lowest mean score was in the z-direction.

A diagrammatic representation of the asymmetry score for the lips using both the clinical midline and Procrustes superimposition at rest, for the mid-point and at maximal smile is shown in Figures 5.1 to Figure 5.8. The non-cleft individual with the highest and lowest asymmetry score is shown in Figure 5.1 to Figure 5.4. In addition, the cleft individual with the highest and lowest asymmetry score is shown in Figure 5.5 to Figure 5.8.

Table 4.5 Asymmetry score of the lips during smiling, using Procrustes superimposition, for the control and cleft groups

		Asymmetry score		x-direction		y-direction		z-direction	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD
Cleft									
	Rest	0.89	0.31	0.56	0.24	0.30	0.11	0.43	0.20
	Median	1.20	0.36	0.77	0.30	0.41	0.15	0.52	0.22
	Maximum	1.29	0.44	0.82	0.34	0.48	0.21	0.55	0.22
Control									
	Rest	0.65	0.18	0.42	0.16	0.23	0.07	0.30	0.12
	Median	0.90	0.32	0.50	0.17	0.41	0.20	0.43	0.21
	Maximum	0.99	0.35	0.57	0.20	0.46	0.22	0.47	0.21

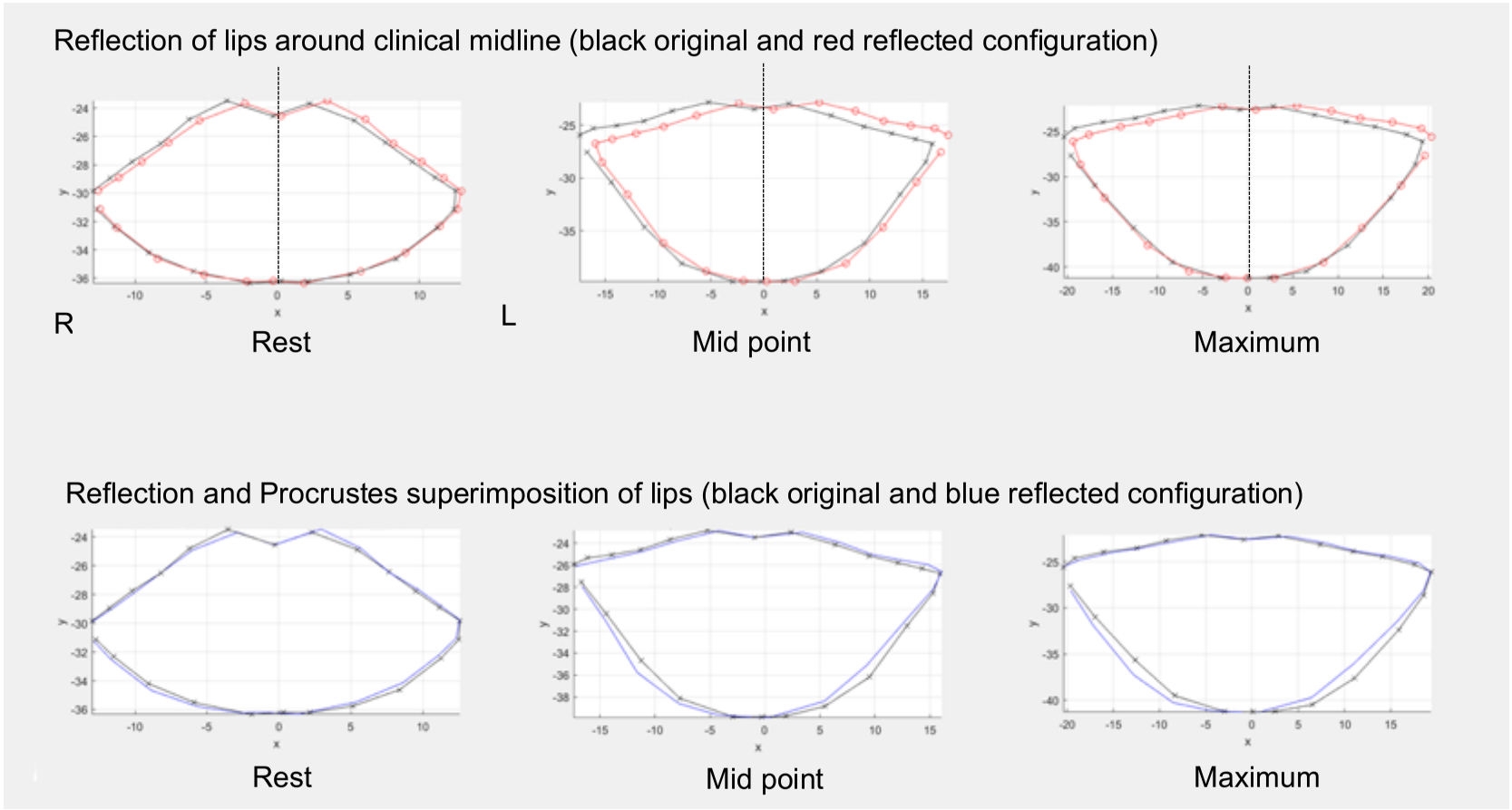


Figure 5.1 Control subject with highest asymmetry score – Front view

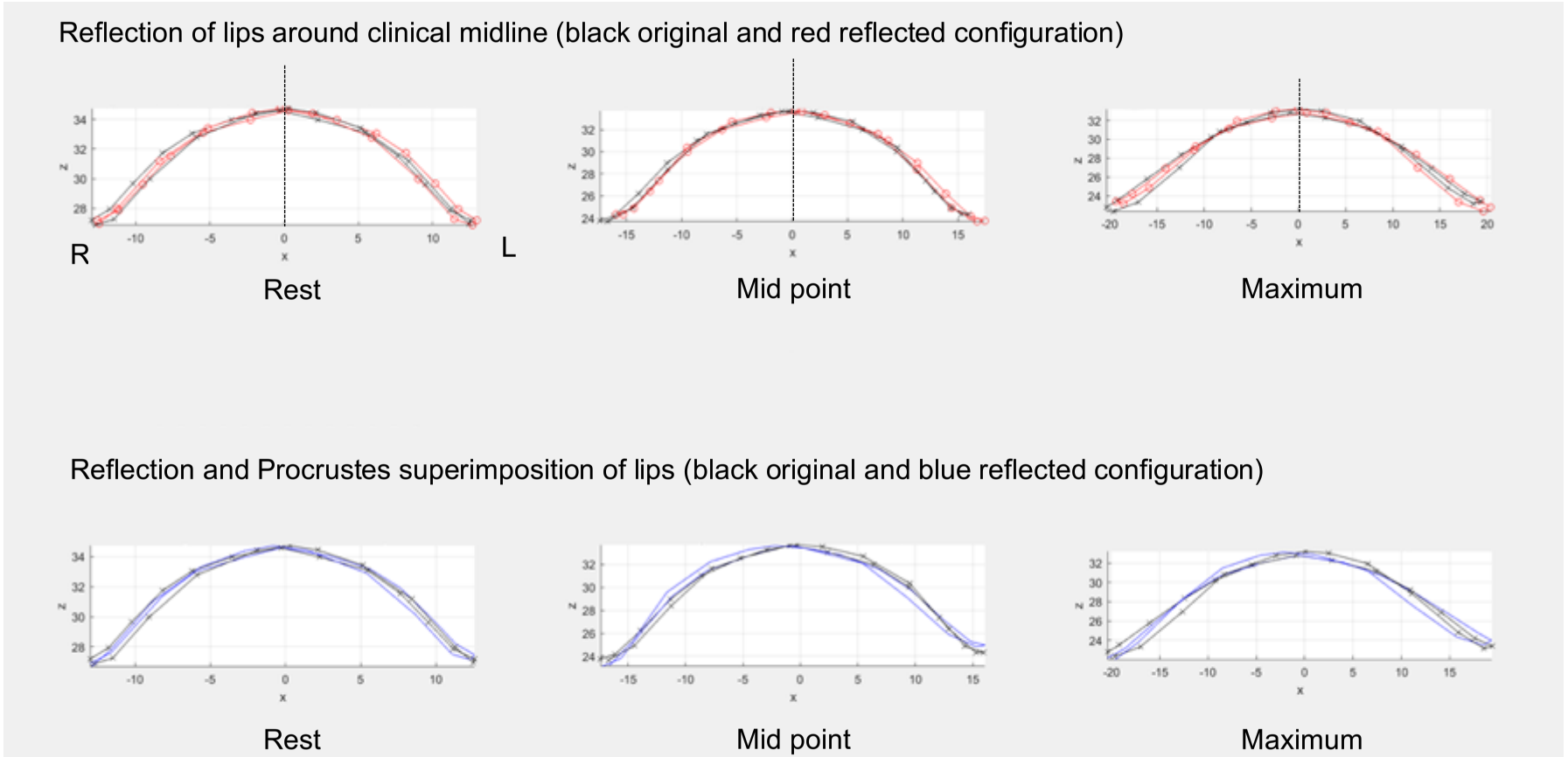


Figure 5.2 Control subject with highest asymmetry score – From below view

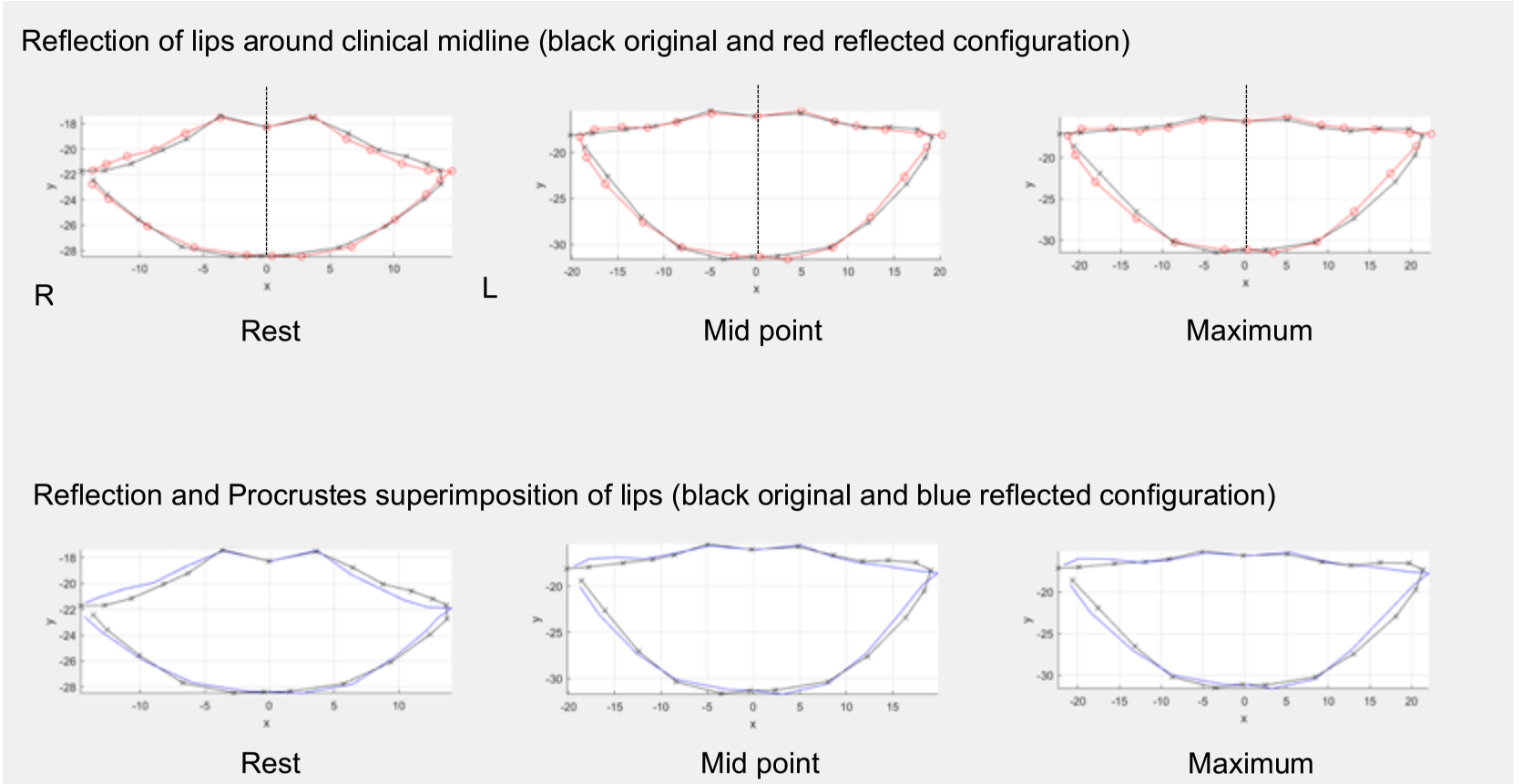


Figure 5.3 Control subject with lowest asymmetry score – Frontal view

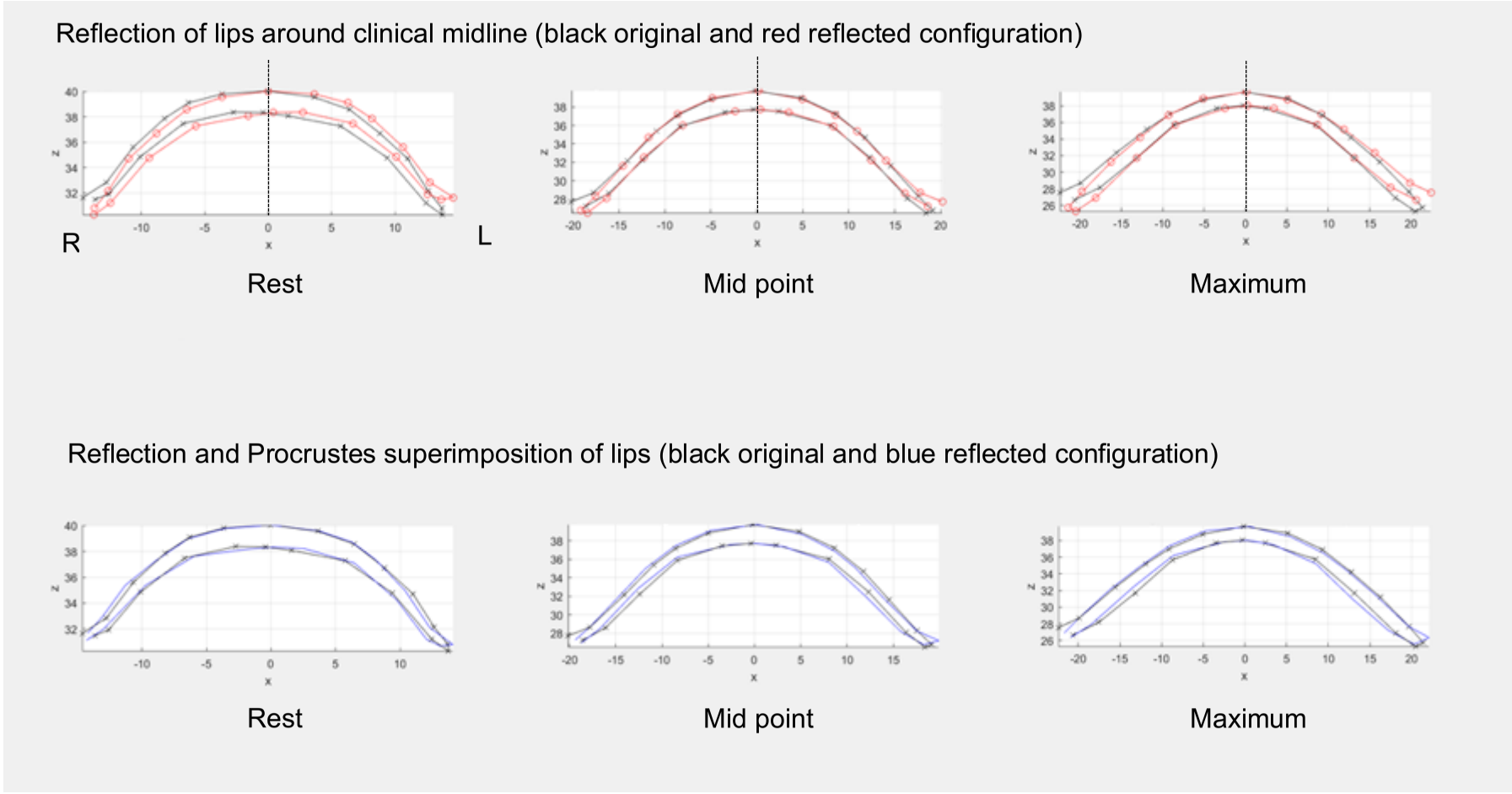


Figure 5.4 Control subject with lowest asymmetry score – From below view

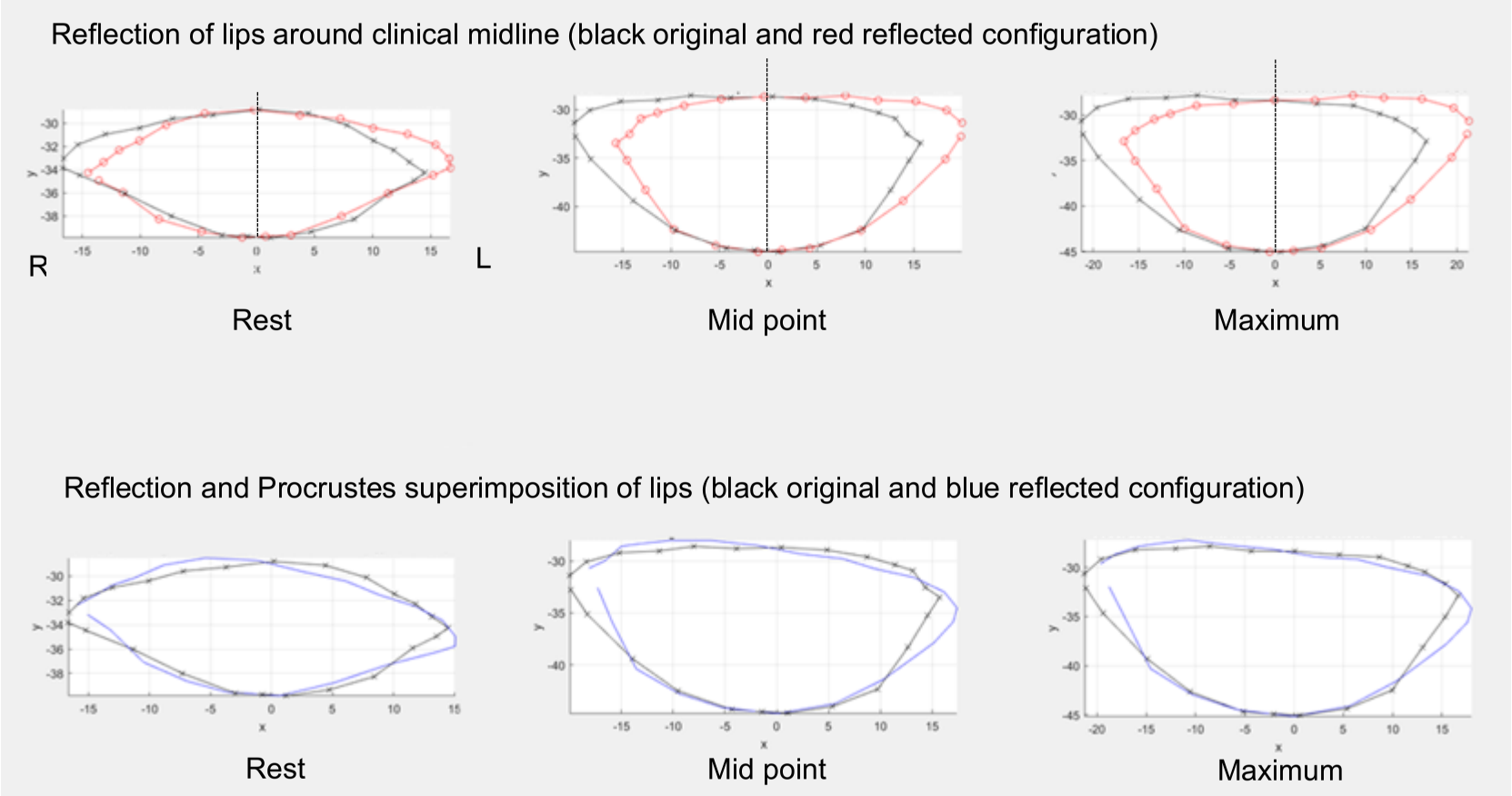


Figure 5.5 Cleft patient with highest asymmetry score – Front view

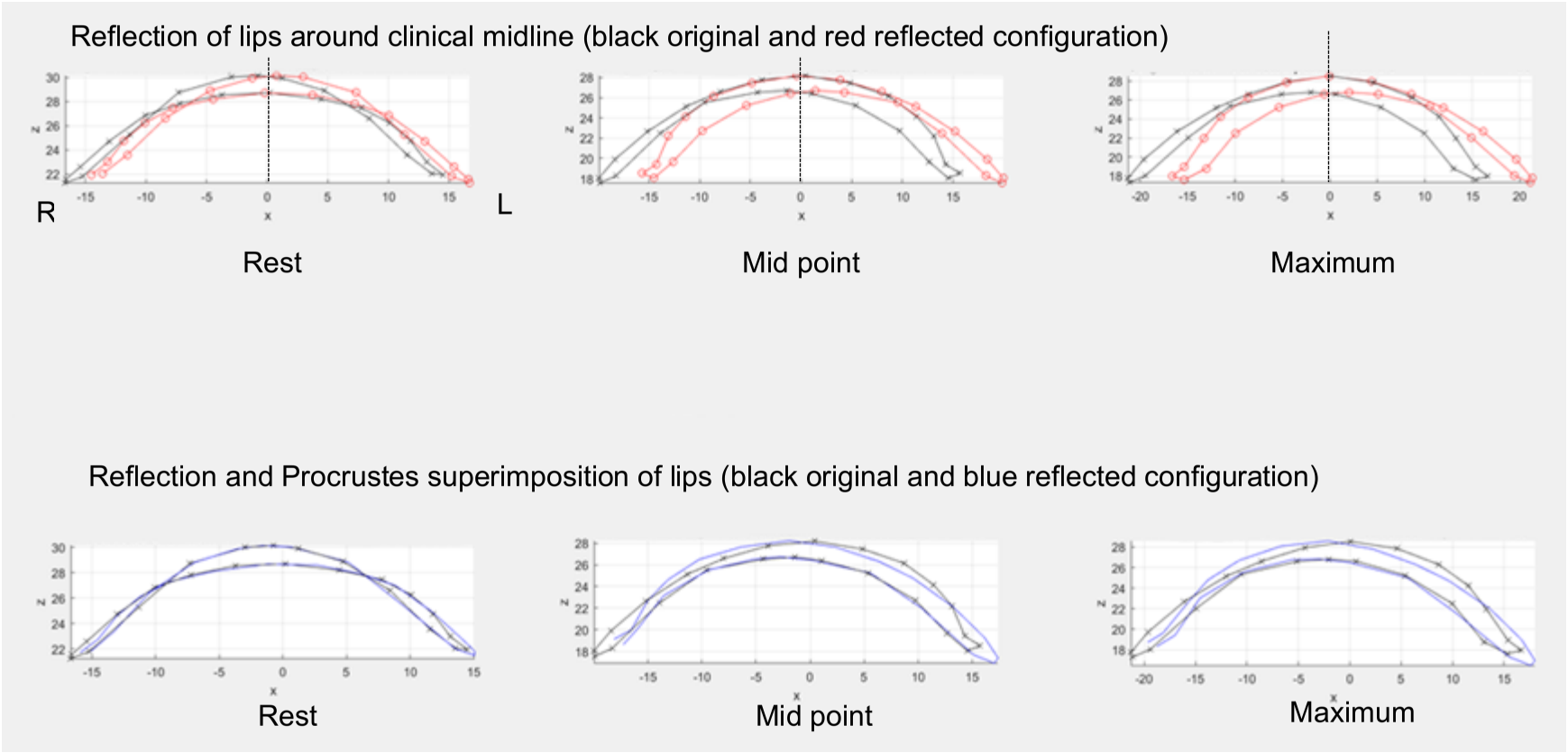


Figure 5.6 Cleft patient with highest asymmetry score – From below view

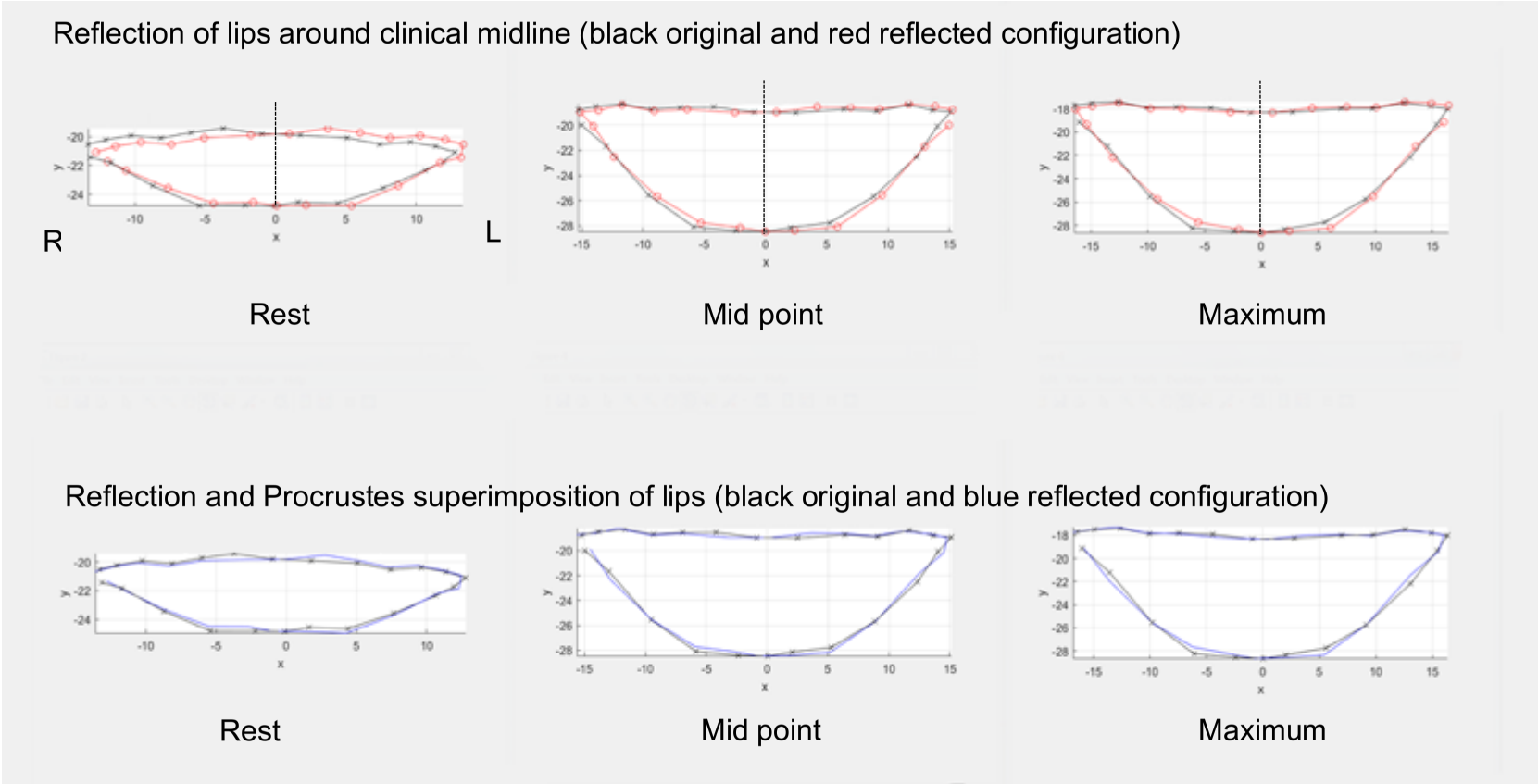


Figure 5.7 Cleft patient with lowest asymmetry score – Front view

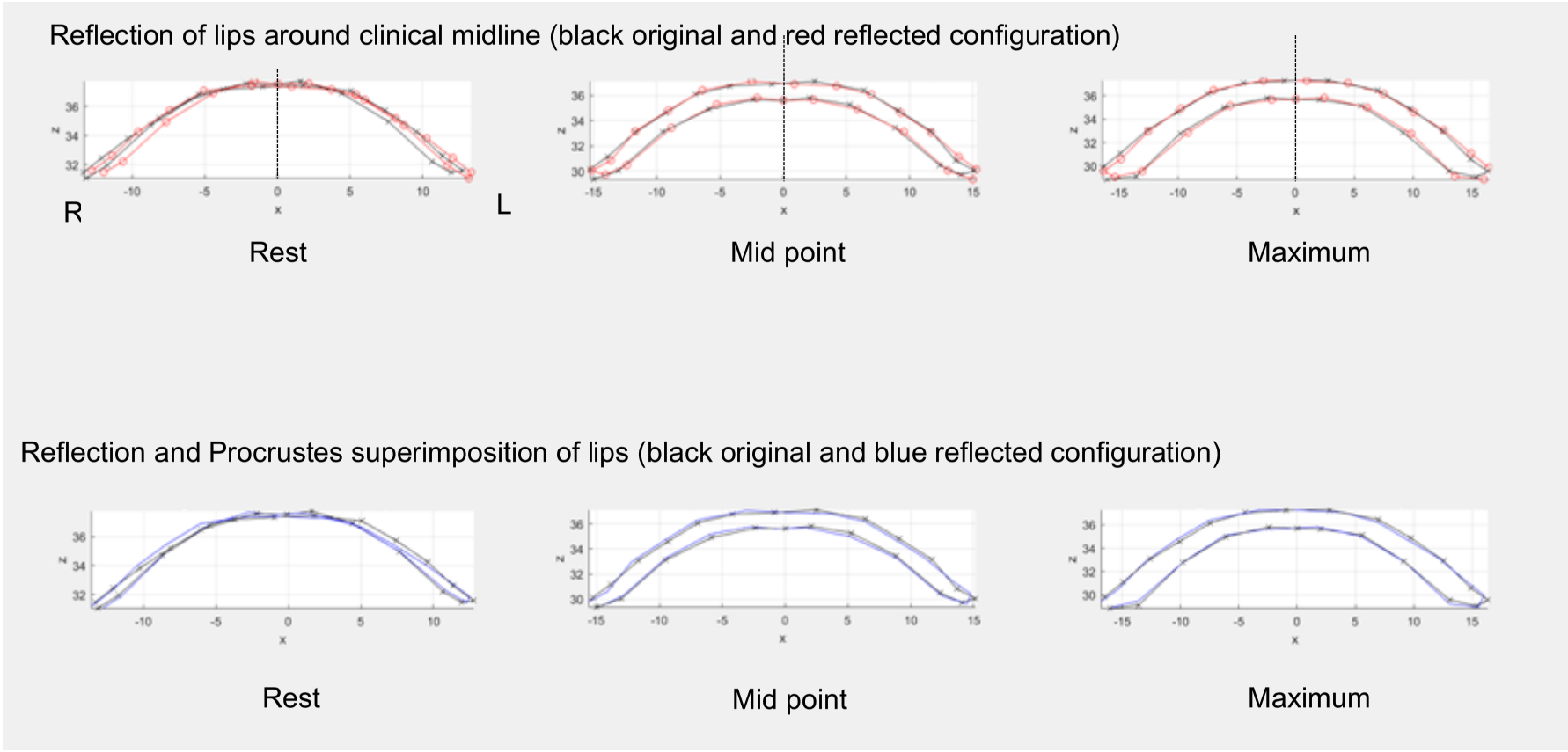


Figure 5.8 Cleft patient with lowest asymmetry score – From above view

4.2 The alar base

4.2.1 Maximum displacement of right (LM15 non-cleft) and left (LM16 cleft) alar bases between the control and cleft groups

In the cleft group, at maximum smile, there was less displacement of LM15 and LM16, in the x, y, z direction and Euclidian distance, compared to the control group, Table 4.6. This was statistically significant ($p<0.05$) only for LM15 in the z-direction and LM16 in the x and z directions. At maximum smile, the displacement of LM15 in the z-direction and LM16 in the x and z directions was between 40-50% less in the cleft group compared to the control group. The 95% confidence interval for the difference in LM16 between the cleft and control group approached 3mm and therefore maybe both statistically and clinically significant.

Within the cleft group the mean absolute differences in absolute displacement of LM15 and LM16 ranged from 0.6mm to 0.9mm, whilst in the control group was 0.5mm to 1.0mm, Table 4.7.

Table 4.6 Maximum displacement of right (LM15 non-cleft) and left (LM16 cleft) alar base for the control and cleft groups

	x-direction		y-direction		z-direction		Euclidian distance	
	LM15	LM16	LM15	LM16	LM15	LM16	LM15	LM16
Control								
Mean (mm)	3.4	3.7	4.3	4.4	1.9	2.1	5.9	6.2
SD (mm)	1.4	1.1	1.4	1.5	0.6	0.8	1.7	1.7
Cleft								
Mean (mm)	2.6	2.2	3.8	4.0	1.1	1.2	4.8	4.9
SD (mm)	1.1	0.8	1.4	1.5	1.0	0.9	1.4	1.5
Differences								
Mean difference (mm)	0.8	1.5	0.5	0.4	0.8	0.9	1.1	1.4
Lower 95% CI for the difference (mm)	-0.2	0.7	-0.5	-0.8	0.1	0.2	-0.2	0.1
Upper 95% CI for the difference (mm)	1.8	2.3	1.6	1.7	1.5	1.6	2.4	2.7
p-value	0.093	**0.001**	0.309	0.469	**0.019**	**0.014**	0.086	**0.039**

Table 4.7 Differences between right (LM15 non-cleft) and left (LM16 cleft) alar base displacement within the control and cleft groups

	Difference between LM15 & LM16							
	x-direction		y-direction		z-direction		Euclidian distance	
	Signed	Absolute	Signed	Absolute	Signed	Absolute	Signed	Absolute
Control								
Mean (mm)	-0.2	0.8	-0.1	0.5	-0.2	0.6	-0.3	1.0
SD (mm)	1.0	0.5	0.7	0.5	0.9	0.6	1.3	0.7
Cleft								
Mean (mm)	0.4	0.9	-0.2	0.8	-0.2	0.6	0.0	0.7
SD (mm)	1.1	0.7	1.0	0.6	0.9	0.6	0.9	0.7

4.2.2 Trajectory of right (LM15 non-cleft) and left (LM16 cleft) alar bases between the control and cleft groups

The Fréchet distance was similar for the cleft group and the control group, Table 4.8.

4.2.3 Symmetry of the alar base when smiling reflecting around the clinical midline

Table 4.9 shows that in the non-cleft control group the mean asymmetry score at rest was 0.76 ± 0.30. From rest to maximum smile, the mean asymmetry score increased to 0.82 ± 0.41, Figure 6.1 and 6.2. In the cleft group, the mean asymmetry score was higher at rest (1.89 ± 0.83), compared to the non-cleft control group and increased to 2.13 ± 1.21 at maximum smile, Figure 6.3 and 6.4. Following a two-sample t-test the differences between the two groups at each time point were statistically significant ($p<0.001$). The upper 95% confidence interval was close to 2.0.

Decomposing the asymmetry scores in the x, y and z directions showed that in in the cleft group, the largest mean asymmetry score was seen in the x-direction, i.e. in a horizontal direction. The lowest mean score was in the y-direction. All the asymmetry scores were higher in the cleft group compared to the control group.

Table 4.8 Trajectory of right (LM15 non-cleft) and left (LM16 cleft) alar base displacement for the control and cleft groups

	Control Group					Cleft Group			
	x	y	z	Euc		x	y	z	Euc
Mean	1.14	0.69	0.93	1.23		1.14	0.98	0.95	1.06
SD	0.39	0.44	0.62	0.65		0.65	0.55	0.48	0.32

Table 4.9 Asymmetry score for the nose when smiling, reflecting around the clinical midline, for the control and cleft groups

		Asymmetry score		x-direction		y-direction		z-direction	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD
Cleft									
	Rest	1.89	0.83	1.41	0.75	0.43	0.56	0.64	0.16
	Median	2.09	1.15	1.50	0.93	0.43	0.30	1.01	0.84
	Maximum	2.13	1.21	1.53	1.00	0.44	0.33	0.99	0.86
Control									
	Rest	0.76	0.30	0.42	0.25	0.20	0.16	0.44	0.31
	Median	0.83	0.40	0.46	0.27	0.21	0.17	0.52	0.42
	Maximum	0.82	0.41	0.48	0.26	0.23	0.15	0.46	0.41

4.2.4 Symmetry of the alar base using Procrustes superimposition between the control group and the cleft group

Table 4.10 shows that in the non-cleft control group the mean asymmetry score was 0.33 ± 0.13 at rest. From rest to maximum smile, the asymmetry score increased to 0.41 ± 0.17, Figure 6.1 and 6.2. In the cleft group, the mean asymmetry score was higher at rest (0.64 ± 0.16), compared to the non-cleft control group and increased to 0.71 ± 0.26 at maximum smile, Figure 6.3 and 6.4. All the asymmetry scores were higher in the cleft group compared to the control group. Following a two-sample t-test the differences between the two groups at each time point were statistically significant ($p<0.001$). The upper 95% confidence interval was close to 0.5.

Decomposing the asymmetry scores in the x, y and z directions showed that in the cleft group, the largest mean asymmetry score was seen in the x-direction, i.e. in a horizontal direction. The lowest mean score was in the y direction.

A diagrammatic representation of the asymmetry score for the nose using both the clinical midline and Procrustes superimposition at rest, for the mid-point and at maximal smile is shown in Figures 6.1 to Figure 6.4. The non-cleft individual with the highest and lowest asymmetry score is shown in Figure 6.1 and Figure 6.2. In addition, the cleft individual with the highest and lowest asymmetry score is shown in Figure 6.3 and Figure 6.4.

Table 4.10 Asymmetry score for the nose during smiling, using Procrustes superimposition, for the control and cleft groups

		Asymmetry score		x-direction		y-direction		z-direction	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD
Cleft									
	Rest	0.64	0.16	0.43	0.13	0.14	0.09	0.32	0.11
	Median	0.69	0.21	0.46	0.19	0.17	0.11	0.36	0.12
	Maximum	0.71	0.26	0.44	0.22	0.20	0.11	0.35	0.13
Control									
	Rest	0.33	0.13	0.21	0.11	0.07	0.03	0.19	0.09
	Median	0.41	0.18	0.28	0.15	0.11	0.05	0.21	0.30
	Maximum	0.41	0.17	0.24	0.14	0.13	0.04	0.22	0.11

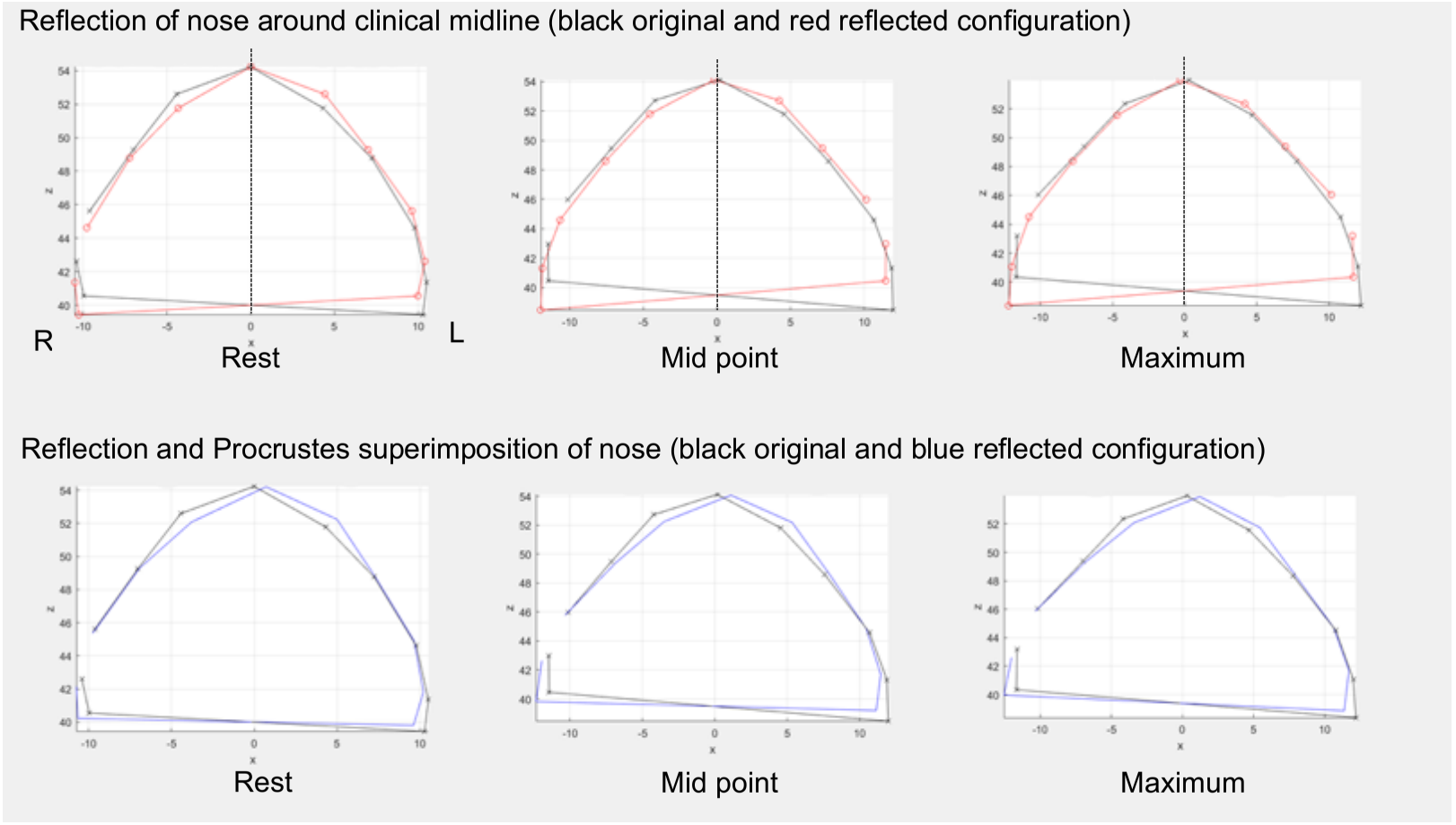


Figure 6.1 Control subject with highest asymmetry score – From below view

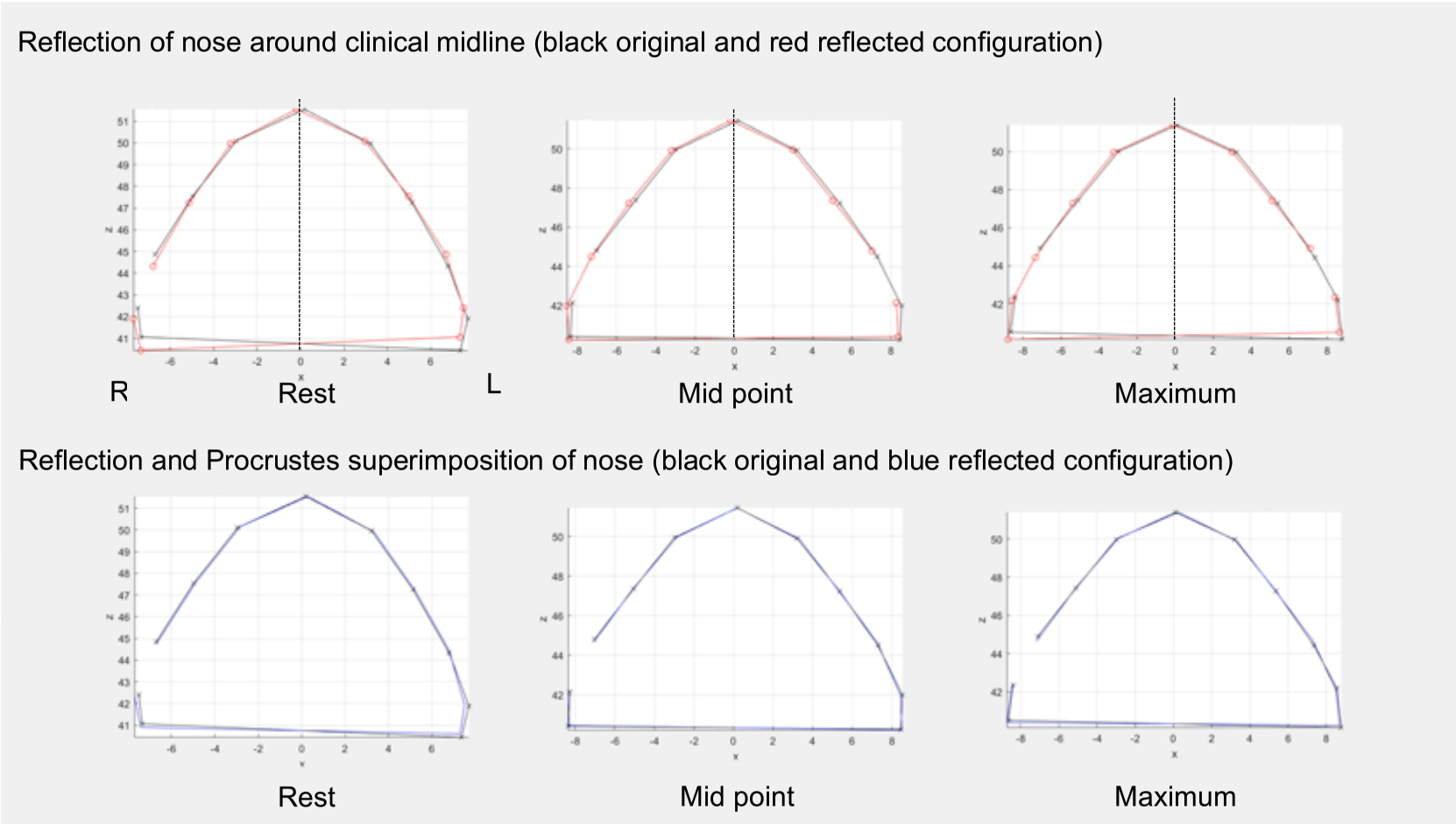


Figure 6.2 Control subject with lowest asymmetry score – From below view

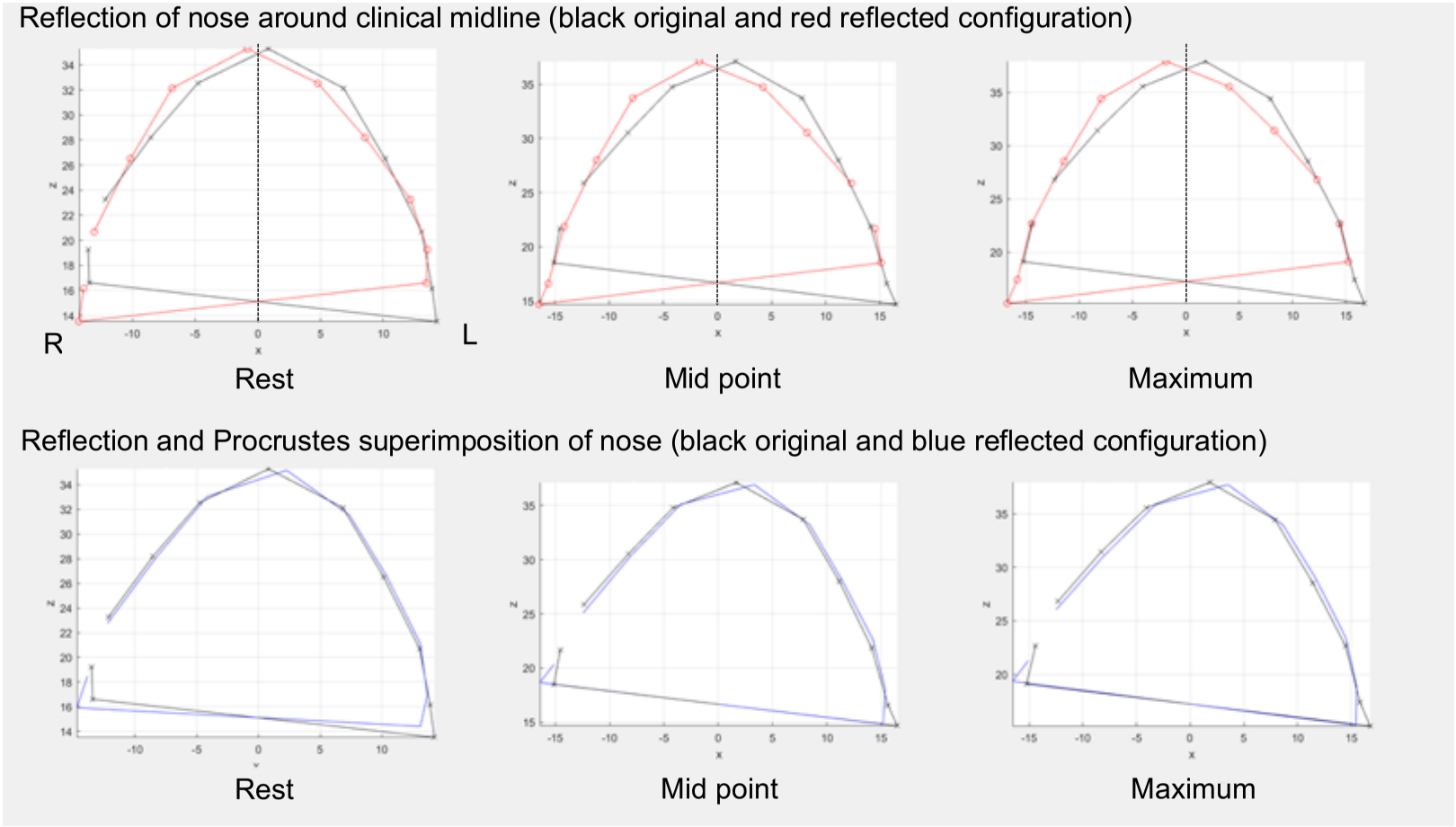


Figure 6.3 Cleft patient with highest asymmetry score – From below view

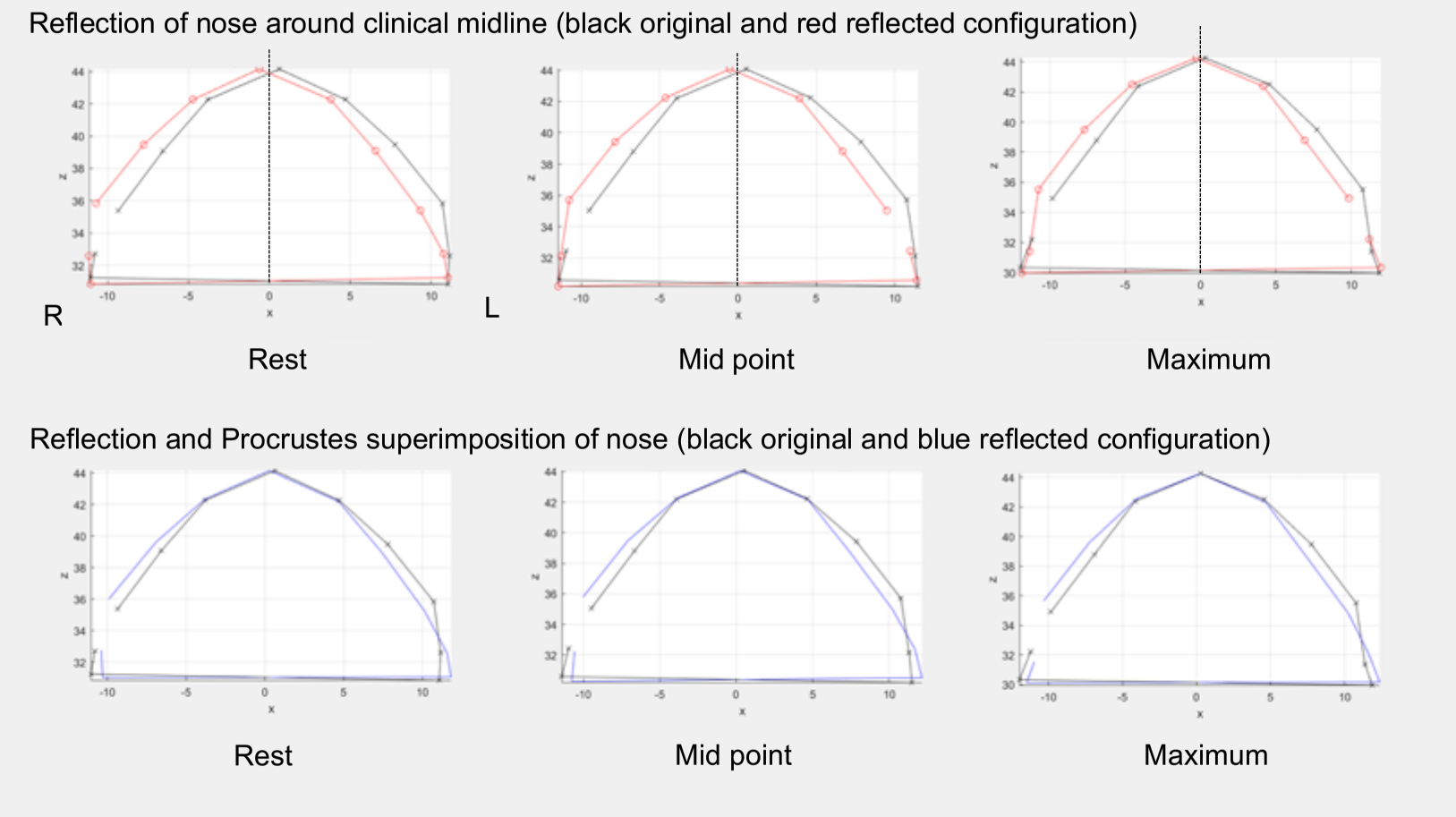


Figure 6.4 Cleft patient with lowest asymmetry score – From below view

4.3 Philtrum of the upper lip

4.3.1 Maximum displacement of right (LM7 non-cleft) and left (LM9 cleft) cristae philtre between the control and cleft groups

Again, at maximum smile, there was less displacement of LM7 and LM9, in the x, y, z direction and Euclidian distance, for the cleft group compared to the control group, Table 4.11. This was statistically significant ($p<0.05$) for LM9 in the x, z-direction and for the Euclidian distance of LM7 and LM9. LM9 moved less in the x and z directions and in Euclidian distance in the cleft group than in the control group. In addition, LM7 also moved less in the z direction and in Euclidian distance compared to the control group. At maximum displacement, the displacement of LM7 and LM9, in the x, y direction and Euclidian distance, was between 50-80% less for the cleft group compared to the control group. However, in the z direction it was only 35-40% of the displacement in the cleft group for both LM7 & LM9. The 95% confidence interval for the difference in LM7 between the cleft and control group approached 3mm in the z direction and Euclidian distance and therefore maybe both statistically and clinically significant. The same was seen for LM9.

When comparing LM7 and LM9 within each group, for symmetry, for the cleft group the mean absolute difference ranged from 1.30mm to 0.28mm, whilst in the control group ranged from 1.14mm to 0.40mm, Table 4.12.

Table 4.11 Maximum displacement of right (LM7 non-cleft) and left (LM9 - cleft) crista philtre for the control and cleft groups

	x-direction		y-direction		z-direction		Euclidian distance	
	LM7	LM9	LM7	LM9	LM7	LM9	LM7	LM9
Control								
Mean (mm)	2.5	2.4	5.5	5.6	6.0	6.0	8.8	8.8
SD (mm)	1.3	1.2	2.3	2.0	1.0	1.1	2.0	1.7
Cleft								
Mean (mm)	1.9	1.3	4.5	4.4	2.4	2.2	5.7	5.2
SD (mm)	1.2	0.7	1.6	1.8	1.8	1.6	2.0	2.1
Differences								
Mean difference (mm)	0.6	1.1	1.0	1.2	3.7	3.8	3.0	3.5
Lower 95% CI for the difference (mm)	-0.5	0.3	-0.6	-0.3	2.5	2.7	1.4	2.0
Upper 95% CI for the difference (mm)	1.6	1.9	2.6	2.7	4.8	4.9	4.6	5.0
p-value	0.27	**0.008**	0.222	0.119	**0.001**	**0.001**	**0.001**	**0.001**

Table 4.12 Differences between right (LM7 non-cleft) and left (LM9 - cleft) crista philtre displacement within the control and cleft groups

	Difference between LM7 & LM9							
	x-direction		y-direction		z-direction		Euclidian distance	
	Signed	Absolute	Signed	Absolute	Signed	Absolute	Signed	Absolute
Control								
Mean (mm)	0.10	1.14	0.09	0.40	0.04	0.44	0.01	0.79
SD (mm)	1.38	0.72	0.65	0.51	0.55	0.31	0.93	0.44
Cleft								
Mean (mm)	0.66	1.30	0.12	0.28	0.21	0.45	0.49	0.71
SD (mm)	1.44	0.86	0.38	0.28	0.54	0.34	0.72	0.49

4.3.2 Trajectory of right (LM7 non-cleft) and left (LM9 cleft) cristae philtre between the control and cleft groups

Table 4.13 shows the Fréchet distance between the two curves produced, of LM7 and LM9, when a graph was plotted of landmark displacement from rest to maximum displacement. Generally, in all directions and Euclidian distance the Fréchet distance was larger for the cleft group than the control group.

This shows that LM7 and LM9 in the control group were associated with a baseline level of asymmetry. LM7 and LM9 in the cleft group also follow different paths, but with an even greater degree of difference than in the control group. The Fréchet distances were generally larger in the cleft group.

Table 4.13 Trajectory of right (LM7 non-cleft) and left (LM9 - cleft) crista philtre within the control and cleft groups

	Control Group					Cleft Group			
	x	y	z	Euc		x	y	z	Euc
Mean	1.58	0.62	0.56	0.98		1.90	0.57	0.67	0.99
SD	0.71	0.43	0.31	0.42		1.11	0.31	0.32	0.39

CHAPTER 5

DISCUSSION

5.1 Discussion

Patients with cleft lip and palate undergo numerous surgical procedures to improve both function and aesthetics. The need to restore function was suggested by Victor Veau, a paediatric surgeon from Paris, leading to the development of the "functional repair" (cited by Bill *et al*., 2006). The aim of the functional repair was to re-establish the continuity and architecture of the nasiolabial musculature to that of a non-cleft individual. Patients undertake a long treatment pathway to achieve the goals of reducing the stigma associated with cleft lip and palate. Several outcome factors of cleft lip and palate repair are measured dynamically or during function; for instance, both speech and swallowing are assessed during function. Surprisingly, facial appearance is assessed statically from conventional photographs (Asher-McDade *et al.,* 1991). This is probably due to the fact technology was not previously available to measure the dynamics of the nasolabial complex, until relatively recently. There are several features of the repair, which may affect the perception of the outcome, for example, the static and dynamic symmetry of the repaired nose and lip, the amount of scarring, the texture and colour of the scar and the continuity of the vermillion border of the upper lip. The purpose of this study was to objectively determine the dynamic movement of the nasolabial complex of adults with unilateral cleft lip ± palate, who had reached the end of their treatment journey, and to compare their outcomes to a non-cleft matched control group. This study specifically investigated the dynamic function and symmetry of the repaired lip and nose.

A certain degree of facial asymmetry exists within the general population, as well as within each individual, and is termed "fluctuating asymmetry" (Lowney *et al*., 2018). For cleft lip and palate patients, the significant points of interest remain around the

nasolabial complex. The simplest objective method of assessing facial symmetry is based on paired bilateral landmarks which represent key anatomical features: left and right cheilion (LM5 and LM11), the philtrum of the lip (LM7 and LM9) and alar bases (LM15 and LM16). Asymmetry would exist if there were differences between these paired points in either the x, y, z direction or in the Euclidian distance. If an asymmetry existed, this could be described as either statistically or clinically significant. Based on previous work by Jones *et al*. (2007), 3mm was determined to be a clinically significant value. However, just because the bilateral landmarks reached the same displacements it does not imply symmetry. An additional requirement for symmetry is that the path the bilateral landmark traverses needs to be similar. In other words, the landmarks need to reach the mirror opposite position in 3D space at the same time, whilst taking the same mirrored path to reach their maximum displacement. In order to measure the path of motion of landmark pairs the Fréchet distance (Fréchet, 1906) was calculated, i.e. a measure of motion symmetry.

As there are various 3D motion capture systems available, broadly categorised as marker-based and marker-free, research has been continually progressing to establish which of the two techniques is most optimal for clinical research. The motion capture system in this study used marker-free technology. Previous studies have used the same marker-free motion capture system to assess the facial dynamics of cleft patients (Bell *et al*., 2014; Hallac *et al*., 2017; Gattani *et al*., 2020). All the studies were consistent with capturing subjects performing a maximum smile expression as this was previously shown to be the most valid and reproducible facial expression (Ju *et al*., 2016). Interestingly, all the previous studies have assessed the outcomes of

primary surgery using paediatric subjects and are therefore limited to assessment of patients who have not completed their overall cleft treatment journey into adulthood.

Participants recruited for the study were between 18-40 years old, and only included patients who had had their unilateral cleft lip ± palate repaired carried out by the Cleft Team at the Queen Elizabeth Hospital, Birmingham using a standardised protocol. The study aims were not to assess the effect of the interventions *per sae,* but were to determine if the final outcome was close to that of a non-cleft group. This is an important difference; just because an intervention has been carried out, it cannot be assumed that the outcome would be “normal”. This can only be known by comparison of the post-intervention group to a “normal” non-cleft group. All individuals in this study were satisfied with their facial outcome and were not seeking any additional surgical intervention. They had therefore reached the end of their treatment journey.

Obviously no participants who had an orthodontic fixed appliance were included in the study, as the appliance may interfere with lip motion. Interestingly, a previous study did include individuals with labial fixed appliances in situ, which may have had an inadvertent effect of the lip dynamics during smiling (Hallac *et al*., 2017). The match control group data were taken from a larger group of volunteers previously collected (Lowney *et al*., 2018). The volunteers were recruited on the basis they had no craniofacial abnormalities, no history of facial surgery, trauma, paralysis or neurological disease. The volunteers were aged between 18-40 years old and excluded if they were undergoing fixed appliance treatment, and if they had a clinically visible facial asymmetry.

The pre-analysis image processing stage is crucial to ensuring facial frames are initially appropriately orientated to the “principal planes”, as if the patient was being assessed clinically. Subsequently, the remaining frames of the sequence were re-orientated to match the initial “anchor frame”. The chosen anatomical landmarks were similar to landmarks used in previous studies to compare the data (Al-Anezi *et al*., 2013; Hallac *et al*., 2017; Gattani *et al*., 2020), including the four landmarks on the forehead used for stabilisation. Analysis of the tracked landmark data can be interpreted and discussed in various ways, as shown by previous studies. Due to the high number of landmarks gathered by automatic tracking, it is easy to “dilute” the asymmetry score, particularly if they are generalised across the whole face (Bell *et al*., 2014; Hallac *et al*., 2017). Gattani *et al*., (2020) acknowledged that using a “total asymmetry score” could potentially reduce the effects of a large asymmetry within the face, if combined with areas of the face that demonstrate very little asymmetry and so presented data on a more local facial region. However, the same problem still applies depending on the site and extent of the region being investigated. The use of “displacement colour maps”, even though useful from a visual perspective, does not allow statistical analysis. The use of Procrustes analysis to determine the asymmetry scores has been explored and demonstrated in numerous previous studies (Bock and Bowman, 2006; Hajeer *et al*., 2004; Bugaighis *et al*., 2010; Bell *et al*., 2014; Hallac *et al*., 2017; Gattani *et al*., 2020). Asymmetry based on the clinical midline is more representative of the clinical situation and reduces the disadvantages of using Partial Procrustes superimposition (Khambay *et al*., 2019). The greater the degree of local facial asymmetry the greater the likelihood the whole facial image will be displaced to achieve the “best-fit”. By using both the clinical midline and Procrustes superimposition, it was possible to separate out the effects of the asymmetry due to

an inherent asymmetry of the structure i.e. lips / mouth and nose and their position relative to the clinical midline. It is possible in a non-cleft individual to have a symmetrical mouth but place it to one side of the midline. In which case, the smile would not look symmetrical even though it was symmetrical. The use of Procrustes superimposition in relation to UCLP patients has previously been discussed by Bock and Bowman (2006). By calculating the Fréchet distance (Fréchet, 1906), the path of motion of paired landmarks can be analysed. This is an innovative application of using the Fréchet distance, to measure the similarity between two curves (Wylie and Zhu, 2014), to analyse data demonstrating clinical anatomically paired landmarks.

5.2 Comparison of the magnitude of displacement of the commissures of the mouth (LM5 and LM11)

For the cleft group, the movement of the corner of the mouth on the cleft side (LM11) was less than the non-cleft side (LM5) in the x, y, z direction and Euclidian distance, and was more pronounced in the x-direction (1.4mm). This may be due to the scarring restricting horizontal movement of the cleft corner of mouth. Compared to the control group, the maximum displacement of the commissures of the mouth (LM5 and LM11) in the x, y, z direction and Euclidian distance, was statistically significantly ($p<0.05$) less in the cleft group. The largest differences were in the z-direction for both commissures of the mouth, which were greater than 3mm, and so were clinically significant in the present sample. This implies that in the cleft group, the commissures of the mouth do not go as far back as in the control group, and again may be due to lip scarring and adhesions. The restricted horizontal movement was also evident between the two groups and the differences would be clinically significant in the larger population, as all upper 95% confidence intervals were above 3mm.

The present study found that during maximum smile, there is between 60-80% less displacement of the commissures of the mouth (LM5 and LM11) for the cleft group compared to the control group. From rest to maximum smile, the control group data shows that the commissures of the mouth move laterally outwards (x-direction), upwards (y-direction) and backwards (z-direction). When compared to the cleft group, all corresponding values were statistically significantly less. Notably, the mean difference between the control group and the cleft group for the left corner (LM11) in the z-direction was 4.7mm (CI 95% 2.4mm to 6.9mm). These findings are consistent when considering facial anatomy and how the muscles of facial expression have been affected after cleft lip repairs. As a result of cleft lip repair, muscles in the nasolabial region will be affected, these include orbicularis oris, levator labii superioris aleque nasi and levator labii superioris. The depressor septi nasi also has a large part to play when pulling the nasal tip downwards (von Arx *et al*., 2018). Constriction of the orbicularis oris muscle and full activation results in pursing and closing of the lips. Therefore, relaxation of the orbicularis oris muscle occurs in order to allow a maximum smile. Two parts to the orbicularis oris, deep and superficial, contribute to the double function of the upper lip. The superficial orbicularis oris muscle is closely related to the other muscles of facial expression and aids retraction of the lower lip (Marur *et al*., 2014). The action of the zygomaticus major fibres, which insert into the levator anguli oris and orbicularis oris, results in elevation of the commissures of the mouth when contracting. Restricted movement of the lip maybe reflective of a disruption of the muscular anatomy in the nasolabial region and results from scarring following primary lip repairs (Trotman *et al*., 2007; Hallac et. al., 2017). The scaring would probably prevent widening of the mouth commissures as well as the backward movement of

the modiolus, as the muscles become “strap-like” and are tighter across the anterior teeth. However, the lip would still be able to elevate as the scar tissue may be running horizontally, and there is possibly more movement in the upper lip soft tissue in the y-direction.

Interestingly, a Le Fort I advancement osteotomy has been show to stretch and changes the orientation of the orbicularis oris and other muscles used to produce facial expressions, which resulted in a decreased magnitude of lip movements (Al-Hiyali *et al*., 2015). This would support the findings of the present study as the end result of either moving the maxilla forward or “tightening” the upper lip as a result of the cleft repair should have similar clinical effects (Al-Hiyali *et al*., 2015). It also suggests that there could be further reduced movement of the upper lip in the cleft group who have undergone a maxillary advancement. It was not the aim of the current study to assess the effects of orthognathic surgery on lip motion following maxillary advancement in a cleft group.

5.3 Comparison of path of motion of the commissures of the mouth (LM5 and LM11)

Based on the Fréchet distance, the commissures of the mouth (LM5 and LM11) did not follow exactly the same path of motion in the control group. This is not surprising, as a certain level of asymmetry would be expected in the general population. This study provides valuable data for the baseline level of asymmetry, based on the path of motion, in a non-cleft control group. The Fréchet distance, in the control group, ranged from 1.18 to 1.57 with a narrow standard deviation and therefore little variability, whilst in the cleft group ranged from 1.45 to 2.56 with a larger variability

(wide standard deviation). The Fréchet distance in the x-direction (horizontally) was close to double for the cleft group compared to the control. This would imply that the horizontal component of the smile is the least asymmetric between the two groups with respect to path of motion. This could be due to the scarring of the lip preventing full lateral expansion of the lip i.e. scarring within orbicularis oris preventing the levator muscles from full lateral expansion. The path of motion of the commissures of the mouth in the anterior-posterior and inferior-superior direction was similar between both groups. Again, this may be explained by the scarring within orbicularis oris running longitudinally but the commissures of the mouth, at the modiolus, can still be pulled back and up, by the levator and zygomaticus major muscles, as they lift the upper lip, much like a curtain. At which point the Fréchet distance becomes clinically significant remains unknown, and beyond the scope of this study.

As expected, the range of motion of the commissures of the mouth were more asymmetric in the cleft group than in the non-cleft group. Previous studies have reported asymmetry of the commissures of the mouth, based on differences in magnitude of landmark displacement, in control groups, at rest and on smiling (Bell *et al*., 2014; Lowney *et al*., 2018). The present study, as well as using landmark displacement, uses path of motion as an outcome measure. In the cleft group, the left and right commissures of the mouth (LM5 and LM11) followed different paths, but also have a larger degree of difference between them. This study supports the previous evidence within the literature that there is restriction and deficiencies of movement when performing facial expressions in cleft groups compared to control groups (Trotman *et al*., 2007; Bell *et al*. 2014; Hallac *et al*., 2017, Al-Rudainy *et al*., 2019, Gattani *et al*., 2020). Additionally, this data presents new information in demonstrating

the path of motion for a normal cohort of patients (obtained from Lowney *et al*., 2018) as well as for a cleft group of patients.

5.4 Symmetry of the lips when smiling reflecting around the clinical midline

This analysis uses the principle that if specified paired bilateral landmarks, around the lips, are reflected around a clinically defined midline, then the differences between the "reflected" landmarks and the original landmarks would be zero if there was perfect symmetry. The "clinical midline" represents the situation if a clinical assessment of the patient had been carried out and is therefore a more valid analysis. A symmetry score of zero is not realistic as "fluctuating asymmetry" between and within individuals has been previously been reported (Thornhill and Gangestad, 1999, Khambay *et al*., 2019). Several possible situations could give rise to the clinical appearance of an asymmetric smile; the smile could be asymmetric and the face symmetrical, the smile could be symmetric but the face asymmetric or both the smile and the face could be asymmetric.

The dynamic capture of maximum smile, in the present study, has determined the asymmetry score at rest, median and maximum frames. In the control group, as the subjects perform a maximum smile, the more asymmetric it becomes. The cleft group demonstrated a higher asymmetry score at rest, which increased over time; the larger standard deviation indicates a larger variation in the group. As with any procedure, though cleft surgery has undergone streamlining of standardised care pathways and operating procedures (Bearn *et al*., 2001; Goodacre and Swan, 2011; Colbert *et al*., 2015) no two cleft patients' outcomes will be identical and each individual would result in a varying level of asymmetry. This may explain the larger difference in standard

deviation within the cleft group compared to the control group. The largest asymmetry scores were seen in the x-direction (horizontally), in both groups. This would coincide with the reduced displacement of the left corner of the mouth (cleft repair) in the group. A recent study found that smile asymmetry increases in all three planes as children with repaired clefts perform a maximum smile (Gattani *et al*., 2020); this residual deficiency obviously continues into adulthood, as supported by data published by Wong (Wong *et al*., 2018). The method presented in the current study decomposed the asymmetry score into the three spacial dimensions to localise the areas that may be clinically deficient. This method of analysis, using the clinically derived midline, produces an asymmetry score that combines the shape of the mouth with its position i.e. it does not differentiate between asymmetric smiles and symmetrical faces, symmetrical smiles and asymmetric faces or both asymmetric smiles and faces. In order to achieve this the mouth itself needs to be analysed irrespective of its position in the face.

5.5 Shape of the mouth irrespective of the face

In this analysis the 3D landmark configuration identifying the lips, was reflected around an arbitrary midline rather than the clinical midline. The reflected landmark configuration is then superimposed over the original landmark configuration and using partial Procrustes superimposition, a “best-fit” of the two configurations is achieved, without rescaling i.e. rotation and translation only. This in effect removes the restraints of the face and aligns the two lips configurations only. This allows a method of assessing the shape of lips in isolation. In both groups, the asymmetry score based on the Procrustes superimposition was less than when the score is based on the clinical midline. This shows that the lips are asymmetric in shape, but they are also

not in the midline of the face in the control group. This should be taken in the context that non-cleft individuals do not have a perfectly symmetrical mouth in a perfectly symmetrical face. In the cleft group, the mouth/lips are not as symmetrical as in the control group at rest or half way through the smile, but are similar at maximum smile. The asymmetry worsens over the duration of the smile; it is larger in the cleft group in all dimensions. The largest scores in both groups was consistently seen in the x-direction, followed by the z-direction and then y-direction. If this is combined with the Fréchet distances, it would suggest that compared to the control group, the repaired cleft group would have a more clinically apparent smile asymmetry.

Decomposition of the feature of interest from the rest of the face has been described in the literature by Bock and Bowman (2006). The feature itself may have an intrinsic asymmetry, which this data is able to quantify by calculating the asymmetry score in isolation, away from the rest of the face. The asymmetry score has been calculated using this method for rest, median and maximum smile frames; this new information provides valuable details on intrinsic asymmetry of the mouth, of a cleft group, when performing a dynamic facial expression.

5.6 Comparison of the magnitude of displacement of the alar bases (LM15 and LM16)

Previous studies have seldom reported on dynamic changes related to the alar base, despite the alar base being significantly affected in cleft patients. This makes the findings of the present study novel but difficult to compare to previous studies. The present study showed that there was less displacement (movement) of the alar bases (LM15 and LM16) in the x, y, z direction and Euclidian distance for the cleft group

compared to the non-cleft control group, in both the affected and unaffected sides of the nose. These differences were statistically significantly different ($p<0.05$) for LM15 in the z-direction and LM16 in the x and z-directions. The mean differences were all less than 2mm in the sample investigated and would therefore not be clinically significant. However, the upper 95% confidence interval for the mean differences between the groups for LM16 in the x-direction was greater than 2mm (2.3mm), which suggests this difference may be clinically significant in the larger population. Compared to the control group, when performing a maximum smile, the displacement of LM15 in the z-direction and LM16 in the x and z directions was between 50-60% for the cleft group. This reduced movement is occurring on an alar base that is already positioned more posteriorly in the z-direction (depressed) in cleft patients (Al-Rudainy *et al*., 2019). The reduced displacement of the alar base, at maximum smile, may be due to restrictions caused by scarring within orbicularis oris muscle, resulting from a primary cleft repair. Levator labii superioris aleque nasi has an insertion to the nasal cartilage, upper lip and at the lateral alar base. Impairment to this muscle results in a deficiency, and results in an inability for the upper lip to be pulled up (Marur *et al*., 2014). Reduced magnitude of displacement in the z-direction could occur for several reasons, for example, due to scar tissue forming in the upper lip after repair, due to a reduction in growth potential, or because of bone resorptive changes occurring in the base of the anterior maxillary alveolus (Liao and Mars, 2005). This demonstrates that in the cleft group, not only are the alar bases more restricted in movement in the x-direction, but remain more depressed within the face in the z-direction compared to the control group. Comparing LM15 and LM16 within each group for symmetry, there is little difference in displacement between the control group (ranges from 0.8-1.0mm) and cleft group (0.6-0.9mm). The lack of asymmetry in displacement is surprising, but

given that the non-affected side of the alar base has reduced movement offers a possible explanation.

5.7 Comparison of path of motion of the alar base (LM15 and LM16)

To date, the Fréchet distance has not been routinely used as a method of analysis to review the path of motion in relation to facial expression. In the control group, LM15 and LM16 do not follow the same path of motion, therefore there is a baseline level of asymmetry associated with the alar base movement during smiling in the normal population. In the cleft group, LM15 and LM16 also do not share the same path of motion, and there is a greater degree of difference, mainly in the y-direction than in the control group. There is little difference in the path of motion in the x and z-direction in the cleft group and control group. Whether the differences in the y-direction in the path of motion are clinically significant remains unknown. Anatomically the nasalis muscle consists of two parts, the upper transverse part and the lower alar part, dilator naris. Dilator naris has an attachment to the alar cartilage of the nose and contraction of this muscle causes the alar to be depressed laterally, resulting in dilation of the nostril (Marur *et al*., 2014). Fibres from this muscle remain relatively untouched in conventional cleft lip nasal repairs, which could be why there is little difference in the path of motion in the x and z directions. In the UK, generally the Millard techniques are used (Madahar *et al*., 2013; McIntyre, 2014); this rotational-advancement technique involves an incision on the medial lip on the cleft affected side, which ascends superiorly through the orbicularis oris and depressor septi (Marur *et al.*, 2014). The area under greatest tension is at the alar base, as the Millard rotation advancement flap is a modified Z-plasty performed at the apex of the cleft (Madahar *et al*., 2013). The tension is a result of lengthening a short medial lip, by dissecting

and re-apposing the orbicularis oris and depressor septi nasi. The incision also extends transversely along the nasal sill (Marcus *et al*., 2017; Madahar *et al*., 2013; Marur *et al*., 2014; von Arx *et al*., 2018). As the lip is stretched transversely, there is restriction in the vertical direction due to this added tension, which could demonstrate why there is a larger difference in the path of motion in the y-direction in the cleft group. The effect of orthognathic surgery, for example a Le Fort I osteotomy, on the alar base in cleft patients could also contribute to an improved path of motion in the z direction.

5.8 Symmetry of the nose when smiling reflecting around the clinical midline

Reflecting the nose around the clinical midline showed that in the control group, there was a pre-existing symmetry at rest, albeit being low (0.76) with a low standard deviation, indicating a small amount of variation. At rest in the cleft group, the asymmetry score was higher than in the control group, and increased with duration of the smile. There was a higher standard deviation within the group, showing more variation. This increased nasal asymmetry in cleft patients compared to a control group at rest, has also been previously reported by Bell *et al*. (2014). This increase in nasal asymmetry with increasing expression was shown to be present in children with repaired clefts, and has now been shown to be a residual deficiency in adults who have completed their cleft journey (Wong *et al*., 2018; Al-Rudainy *et al*., 2019; Gattani *et al*., 2020). Decomposition of the scores demonstrated similar differences in x, y and z directions between the cleft and control groups. However, in the z-direction, there was less of an asymmetry when performing a maximum smile compared to the median frame during the smile. Both groups demonstrated the largest asymmetry scores in the x-direction. The asymmetry scores were approximately 3.5 greater in the cleft group in the x-direction at rest, median and maximum frames. The contraction action

of levator anguli oris results in the corner of the mouth being raised, which contributes to the deepening of the nasolabial furrow in a diagonal direction. This, in combination with elevation of the medial and lateral aspects of the levator labii superioris alaque nasi, results in more significant changes in the x-direction (von Arx *et al*., 2018). Asymmetry in the x-direction contributes the most to the overall asymmetry score at rest and then this continues during maximum smile expression. The nose is wider in cleft patients with the affected alar base being displaced to the non-cleft side (Bell *et al*., 2014, Al-Rudainy *et al*., 2019).

5.9 Shape of the nose ignoring the face

Reflecting around an arbitrary midline and following Procrustes superimposition (allowing rotation and translation), the control group demonstrated a low asymmetry score at rest. The asymmetry score increased during the maximum smile expression. In the cleft group the asymmetry scores were higher at rest than the control group, and the asymmetry score increased with maximum smile. The largest asymmetry scores were seen in both groups in the x-direction. The anatomy of the nose is affected in cleft patients due to nasal components being influenced by hypoplasia of the maxillary segments. Components affected include the nasal dome, the columella, the alar base, the nasal septum and medial and lateral crus of the alar cartilage. The lower lateral cartilage demonstrates asymmetry as is it commonly displaced laterally and inferiorly on the cleft side, in an unrepaired cleft. When repaired the alar cartilage is dissected and translated into a normal position, i.e. translated towards the non-cleft side, the transverse part of the nasalis, which passes the alar base around the lateral aspect of the nose, is stretched (Salyer *et al*., 2005). On the cleft affected side, this may result in residual asymmetry transversely (in the x-direction) associated with the

alar base if the nasalis is translated inwards, restricting movement in the x-direction during dynamic facial expression.

The asymmetry scores are higher when the nasal landmarks are reflected around the clinical midline compared to using Procrustes superimposition. This suggests that the nose is inheritably asymmetric and this is further accentuated by the fact that the nose is not positioned symmetrically in the face, relative to the midline. In addition, the nasal shape becomes more asymmetric during smiling.

5.10 Comparison of displacement of the philtrum of the lip (LM7 and LM9)

The magnitude of displacement of the right (LM7) and left *crista philtre* (LM9) in the x, y, z direction and Euclidean distance were statistically significantly less in the cleft group than the control group ($p<0.05$), LM9 (affected side in cleft patients) moved less in the x and z direction, and in the Euclidian distance. Previous studies have reported on the upper lip movement as a whole by grouping together five landmark pairs (Hallac *et al*., 2017). Given the various anatomical components of the upper lip, using this "grouping technique" of landmarks, there was less potential to identify which specific points of the upper lip were being displaced more or less during smiling. The present study quantified the amount of displacement in x, y, z and Euclidian distance for the philtrum of the lip with greater accuracy than previous studies (Bell *et al*., 2014; Hallac *et al*., 2017; Gattani *et al*., 2020). Within the cleft group, the maximum displacement of LM9 was less in the z direction compared to the control group. This reduced movement was on top of the substantial deviation of the philtrum to the cleft affected side previously reported (Al-Rudainy *et al*., 2019). Contraction of zygomaticus major and zygomaticus minor causes a diagonal displacement of the commissures of the mouth, thus stretching the lips, and causing the philtrum of the lip to be displaced in a

lateral direction (Marur *et al*., 2014). Scarring of these muscles in the immediate vicinity will prevent the philtrum from moving posteriorly (z-direction) as it contacts the anterior teeth and is similar to the commissures of the mouth.

5.11 Comparison of path of motion of the philtrum of the lip (LM7 and LM9)

When reviewing the Fréchet distance in relation to the philtrum of the lip, it was identified that within the control group, LM7 and LM9 do not follow the same path of motion. Coincident with other facial features, this shows that there is a baseline level of asymmetry. There is a varying path of motion of the philtrum in the cleft group in comparison to the control group, with larger values for the Fréchet distance in x and z directions and Euclidian distance, but not in the y direction. The largest Fréchet distance was found in the x direction in the cleft group. There are numerous muscle insertions at the medial philtrum ridge; zygomaticus major and minor, orbicularis oris, levator labii superioris and the superficial reticular fibers of the levator labii superioris alaeque nasi (Chopan *et al*., 2017). As a cleft lip repair is highly sensitive to the muscles listed, any amount of scarring is likely to affect the dynamic motion of the philtrum of the lip on the cleft affected side, which was demonstrated in the data shown, particularly in the x and z directions.

5.12 Limitations of the study

The study itself contributes new information to the literature by presenting results of dynamic facial expression of a control group compared with an adult cleft group at the end of their treatment journey. To date, no other 3D motion capture study with adult cleft patients on completion of their treatment has been published within the literature.

The difficulties, however, remain in gaining continuity of studying this particular cohort of patients. The sample size of the cleft cohort was lower than anticipated. CLP patients have been committed to attending multi-disciplinary appointments since birth into adolescence and on into adulthood. This study aimed to analyse the dynamic facial expression of their maximum smile at the end of their treatment journey. Recruitment of UCLP patients after their "final" discharge appointment from the adult cleft clinic or "retainer review" clinic at Queen Elizabeth Hospital, Birmingham, proved difficult in engaging patients to participate. One of the main barriers to this was having the patients attend a follow-up appointment at another site (Birmingham Dental Hospital) for the 3D motion capture, despite the simple imaging capture process.

Using the Di4D capture system, as mentioned in previous studies (Hallac *et al.*, 2017; Lowney *et al*., 2018; Al-Rudainy *et al*. 2019; Gattani *et al*., 2020) the large volume of data captured can be daunting and difficult to decide how best to analyse. With the generic mesh being able to create a known 3076 vertices per frame, these individual landmarks generate highly specific, but large volumes of data.

There are various methods of analyses used in published literature, all of which have not been used within this study. Bock and Bowman (2006) discussed analysing asymmetry in shape curves, which was used in published study by Bell *et al*., (2014). However, limitations to this method included difficulties in analysing rotations of curves in three dimensions, which becomes challenging when considering dynamic facial expression. To remain consistent with dynamic facial expression, the Fréchet distance was used to analyse path of motion during a maximum smile. As this is a novel

approach to analysing data in the three planes and Euclidian distance, there are no previous studies which use this analysis to compare the data to.

Using data from the control group by Lowney *et al*. (2018), this study was useful to analyse the Fréchet distance of various facial landmarks of interest and comparing them to the cleft group. This analysis could be useful to review data of patients who have had other interventions, e.g. bilateral CLP patients, patients with a facial paralysis or patients with neurological disorders. Despite the high-volume of data capture that is achievable, the Di4D system for three-dimensional motion capture remains an innovative, accurate and objective tool to assess dynamic facial expressions.

CHAPTER 6

CONCLUSIONS

6.1 The null hypothesis is rejected

The null hypothesis is rejected as there was statistically ($p<0.05$) and clinically significantly (>3mm) less displacement (Euclidian distance) of the corners of the mouth in cleft patients compared to the non-cleft group.

In addition, this difference was greater for LM11 (cleft) in the x and z directions and Euclidian distance than for LM5 (non-cleft). There is a greater difference in displacement between the left and right corners of the mouth in the cleft group compared to the non-cleft group.

6.2 Secondary outcome measures

6.2.1 Commissures of the mouth - LM5 (non-cleft) & LM11 (cleft)

- The corners of the mouth did not follow the same path of displacement as one another in both groups, but was more pronounced in the cleft group.
- Based on the Procrustes derived asymmetry score, the shape of the mouth is different between normal and cleft patients at rest and at median smile, but is similar at maximum smile.
- There was an increase in asymmetry score from rest to maximum smile in both groups; this was greater in the cleft group.
- As the asymmetry scores were larger using the clinical midline rather than the Procrustes method, this would suggest that the lips were similar in shape but orientated differently in the face of cleft patients.

6.2.2 The alar base - LM15 (non-cleft) & LM16 (cleft)

- There was statistically ($p<0.05$) less displacement (Euclidian distance) of the right and left alar base in cleft patients compared to the non-cleft group; this was not clinically significant (>3mm). This difference was greater for LM16 (cleft) in the x and z directions and Euclidian distance than for LM15 (non-cleft).
- The difference in displacement between the left and right alar bases were similar in the cleft group than in the non-cleft group.
- LM15 & LM16 followed a similar path of displacement as one another in the cleft group and non-cleft groups.
- Based on the Procrustes derived asymmetry score the shape of the nose is different between normal and cleft patients.
- As the asymmetry scores are different, and larger, between the clinical midline and Procrustes method, this would suggest that the alar bases are orientated differently in cleft patients.
- There was an increase in asymmetry score from rest to maximum smile in both groups; this was greater in the cleft group.

6.2.3 Philtrum of upper lip - LM7 (non-cleft) & LM9 (cleft)

- There was less displacement (Euclidian distance) of right and left crista philtre in cleft patients compared to the non-cleft group. This was statistically ($p<0.05$) and clinically significant (>3mm). This difference was greater for LM9 (cleft) in the x and z directions and Euclidian distance than for LM15 (non-cleft). This was statistically ($p<0.05$) and was clinically significant (>3mm) for LM7 and LM9 in both the z directions and Euclidian distance.

- The difference in displacement between the left and right crista philtre were similar in the cleft group than in the non-cleft group.
- In both groups, LM7 & LM9 did not follow the same path of displacement as one another, but this more pronounced in the cleft group, especially in the x-direction.

CHAPTER 7

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CHAPTER 8

APPENDICES

8.1 Research Ethics Committee approval

NHS
Health Research Authority

North West - Preston Research Ethics Committee
Barlow House
3rd Floor
4 Minshull Street
Manchester
M1 3DZ

Tel: 020 71048008

Please note: This is the favourable opinion of the REC only and does not allow the amendment to be implemented at NHS sites in England until the outcome of the HRA assessment has been confirmed.

16 October 2017

Professor Balvinder Khambay
Professor / Honorary Consultant in Orthodontics
University of Birmingham
Floor 3, School of Dentistry
University of Birmingham
5 Mill Pool Way
B5 7EG

Dear Professor Khambay

Study title:	**A pilot study to assess the outcome of dynamic lip function of cleft patients following final surgical correction.**
REC reference:	**16/NW/0594**
Amendment number:	**2**
Amendment date:	**08 September 2017**
IRAS project ID:	**208383**

Change of sponsor and site, change to start and end dates, increase in sample size, new site

The above amendment was reviewed by the Sub-Committee in correspondence.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

The members had no ethical issues with this amendment.

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Covering letter on headed paper		01 October 2017
Evidence of Sponsor Insurance or Indemnity (non NHS Sponsors only)		
Evidence of Sponsor Insurance or Indemnity (non NHS Sponsors only)		
Evidence of Sponsor Insurance or Indemnity (non NHS Sponsors only)		
Notice of Substantial Amendment (non-CTIMP)	2	08 September 2017
Other [Prof K]		
Other [IRAS form signed by new sponsor]		
Participant consent form	4	25 July 2017
Participant information sheet (PIS)	5	25 July 2017
Research protocol or project proposal	3	25 July 2017

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

Working with NHS Care Organisations

Sponsors should ensure that they notify the R&D office for the relevant NHS care organisation of this amendment in line with the terms detailed in the categorisation email issued by the lead nation for the study.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

We are pleased to welcome researchers and R & D staff at our Research Ethics Committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

16/NW/0594:	**Please quote this number on all correspondence**

Yours sincerely



Dr Rob Monks
Chair

E-mail: nrescommittee.northwest-preston@nhs.net

Enclosures: *List of names and professions of members who took part in the review*

Copy to: *Miss Priti Parmar, Birmingham Comunity Healthcare NHS Foundation Trust*
Sean Jennings, University of Birmingham

North West - Preston Research Ethics Committee

Attendance at Sub-Committee of the REC meeting on 16 October 2017

Committee Members:

Name	*Profession*	*Present*	*Notes*
Professor Carol Haigh	Professor of Nursing	Yes	
Dr Rob Monks	Principal Lecturer in Nursing, Research and Innovation Lead	Yes	

Also in attendance:

Name	*Position (or reason for attending)*
Mrs Carol Ebenezer	REC Manager

8.2 Patient invitation to participate

NHS
University Hospitals Birmingham
NHS Foundation Trust

Birmingham Community Healthcare NHS
NHS Trust

UNIVERSITY OF BIRMINGHAM

CONFIDENTIAL WHEN COMPLETED

Date of letter

<Name>
<Street>
<City>
<Postcode>
<Date>

Dear < name>

INVITATION TO TAKE PART IN RESEARCH TO COMPARE THE QUALITY OF SMILES IN TREATED CLEFT LIP AND PALATE ADULTS WITH A NON-CLEFT GROUP OF ADULTS.

Researchers from the University of Birminghamare currently running a research study, "A pilot study to assess the outcome of dynamic lip function of cleft patients following final surgical correction", comparing the quality of smiles in treated cleft lip and palate adults with a non-cleft group of adults. From our records, it looks like you may be suitable to take part in this research. Before you decide if you would like to take part it is important for you to understand why the study is being done and what it will involve. Please take time to carefully read the accompanying Patient Information Sheet.

You are under no obligation to take part and your usual standard of care will be maintained whether you decide to take part or not. Even if you decide to take part, you are still free to withdraw from the research at any time.

If you would like to take part please complete and return the Informed Consent form (enclosed with this letter) to Professor Khambay's research team and they will contact you to arrange an appointment.

You will be reimbursed for your travel expenses and parking charges when you attend your appointment. The appointment will be at the Birmingham Dental Hospital and School, 5 Mill Pool Way, Birmingham, B5 7EG.

Alternatively to find out more information you can contact the researchers in one of the following ways:

1) Send back page 3 of this letter in the stamped addressed envelope provided to the following address:

   Professor Khambay
   Orthodontic Department
   Birmingham Dental Hospital & School
   5 Mill Pool Way,
   Birmingham,
   B5 7EG.

2) Contact the Research Team on:

Tel No.: 0121 466 5470 E-mail: b.s.khambay.1@bham.ac.uk

Thank you for taking the time to consider this.

Yours sincerely
Mr Ian Sharp (Consultant Cleft and Maxillofacial Surgeon, Clinical Lead)
Mr Lars Enocson (Lead Orthodontist West Midlands Regional Cleft Service)

Enc

1. Patient Information Sheet
2. Informed Consent form
3. Stamped addressed envelope

NHS
University Hospitals Birmingham
NHS Foundation Trust

Birmingham Community Healthcare NHS
NHS Trust

UNIVERSITY OF BIRMINGHAM

PLEASE COMPLETE THIS PAGE AND RETURN

FOR THE ATTENTION OF:

Professor Khambay
Orthodontic Department
Birmingham Dental Hospital & School
5 Mill Pool Way,
Birmingham,
B5 7EG

☐ I am not interested in taking part in the study

☐ I have enclosed the signed consent form; please contact me for an appointment.

☐ I might be interested in taking part in the study and would like to hear more about it

For the patient:

Please indicate your answer by ticking the appropriate box below.

THANK YOU for taking the time to consider this.

INVITATION TO TAKE PART IN RESEARCH

Please sign below:

Signature:_____ Date_____

Please write your address and best method of contact here:

8.3 Patient information sheet

UNIVERSITY OF BIRMINGHAM | SCHOOL OF DENTISTRY

Birmingham Community Healthcare NHS
NHS Foundation Trust

IRAS No: 208383

Study title
A pilot study to compare the quality of smiles in treated cleft lip and palate adults with a non-cleft group of adults.

Invitation and brief summary
You are being invited to take part in a research project. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us / me if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Using digital video cameras we want to take a 3-5 second video clip of you smiling. We have computer software that can analyse your smile, and determine for instance if it is symmetrical. We want to see if smiles of patients who have had surgical repair of their cleft lip (and palate), and are towards the end of their treatment, are the same as non-cleft individuals. This will show if there are any differences and we can then think about how we can improve the outcome of future patients as a result of what we find.

Why have I been chosen?
We are looking for 50 patients between the ages of 18 and 40 who have had surgical repair of their cleft lip (and palate) and are towards the end of their surgical treatment.

What's involved?
You will recall that as part of your previous clinical appointments you will have been sent to have some facial photographs taken for your medical records. The equipment for this study is in the same Department i.e. Medical Illustration. So immediately before or after you have had the normal photographs taken the short video clip will also be taken. No additional appointments are necessary. This video recording as with the conventional photographs form part of your medical records.

During the videoing you will be asked to perform two different smiles, one with your lips together and the other saying "cheese". We will demonstrate the two different types of smiles and you will have time to practice them. When you are ready we will take a 3-5 second video clip of you smiling.

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep (and be asked to sign a consent form) and you can still withdraw at any time without it affecting any treatment that you are entitled to in any way. You do not have to give a reason.

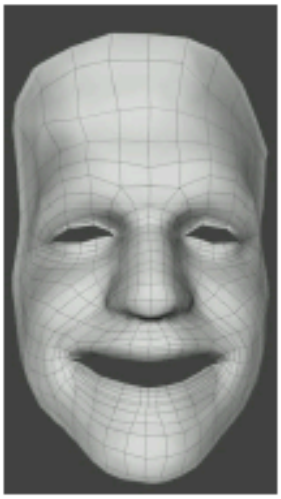
We may use your anonymized data from this study for future research projects.

Will my taking part in this project be kept confidential and what will happen to the results of the research project?
The video image (a still image is shown on the next page) will be stored as part of your routine medical records. Only clinical staff involved in your care and only the researchers involved in this study will know you have taken part.

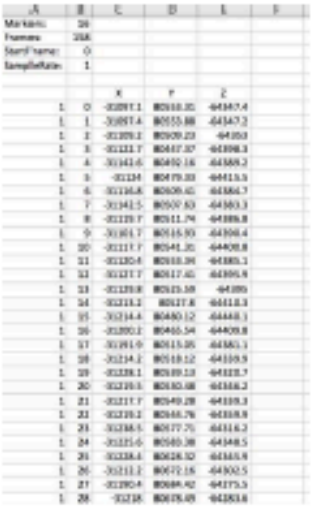
The photographs can be displayed in a variety of different ways – video image and mesh.



Still image from the video image which forms part of your records.



Mesh used for analysis.



Numerical data used for analysis.

Still pictures of your face taken from the video image will not be used in publications unless you have specifically agreed for them to be used. We will contact you and ask your permission.

However we would like to seek your permission to use the video clip in presentations to fellow researchers and clinicians who are also interested in this technology.

The video image will be used to produce the mesh and the numerical data. The research team will use the mesh and numerical data only.

What will happen to the results of the study?
The main findings will be written up and submitted to an appropriate scientific journal; again your facial images will not appear in the journal unless formal approval has been obtained.

What are the possible benefits of taking part?
We cannot guarantee any specific treatment benefits to you directly. However, we would hope this research delivers wider benefits to society and others with a similar condition.

What are the possible disadvantages and risks of taking part?

There are no physical risks in participating in this research project. Your video image will be stored with your clinical notes and will only be shared with researchers interested in the technology used to make the mesh and numerical data with your consent.

Contact for further information

If you have any further queries or complaints about this study please do not hesitate to contact the individual via the email address supplied below.

Professor Balvinder Khambay

[redacted]

Birmingham Dental Hospital

School of Dentistry

Mill Pool Way

B5 7EG

Or

Dr Naomi Hubber

Clinical Research Facilitator

dentistryresearch@contacts.bham.ac.uk

This study has been reviewed and given a favourable opinion by North West-Preston on 02 August 2016, ethics reference 16/NW/0594.

8.4 Patient consent form

UNIVERSITY OF BIRMINGHAM | SCHOOL OF DENTISTRY

Birmingham Community Healthcare NHS

IRAS No: 208383

Job Number:

CONSENT FORM

Title of project: A pilot study to assess the outcome of dynamic lip function of cleft patients following final surgical correction.

Name of Researcher: Professor Balvinder Khambay

Please initial box

1. I confirm that I have read the information sheet dated 25th July 2017 (version 5) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand that the information collected about me will be used to support other research in the future, and may be shared anonymously with other researchers. ☐
4. I confirm that my video clip can be used in presentations to fellow researchers and clinicians who are also interested in this technology. ☐
5. I agree to be contacted by the researcher to seek permission to publish my facial image in a scientific journal. ☐
6. I agree to take part in the above study. ☐

Name of Participant	Date	Signature
Name of Person taking consent	Date	Signature

A pilot study to assess the outcome of dynamic lip function of cleft patients following final surgical correction.		
Consent Form	Version 4	25th July 2017

When completed: 1 for participant; 1 for researcher site file; 1 (original) to be kept in medical notes.